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# CARCINOGENIC BIOASSAYS ON AIR POLLUTANTS

W. C. Hueper, et al

National Cancer Institute
Bethesda, Maryland

1960

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Public Health Service
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# Carcinogenic Bioassays on Air Pollutants

W. C. Hueper*, P. Kotin**, E. C. Tabor***, Wm. W. Payne*, H. Falk**, and E. Sawicki***

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The marked and progressive rise in frequency of lung cancers observed since the turn of the century in many industrialized countries has become a matter of general concern. It is important that this development has exhibited a remarkable degree of irregularity not only concerning the time of its onset in different countries and in different population groups, i.e., especially urban and rural populations and members of the two sexes, but also regarding the progression rate of incidence of lung cancers as well as their age distribution in different countries and regions of individual countries (Hueper). The following figures and tables briefly illustrate these phenomena (tables 1-8, figs. 1-7).

Fig. 1 shows graphically the marked but proportionally differing rise in the lung cancer death rates of several countries (England and Wales; Switzerland; United States and Norway) during the last 33 years.

Tables 1 and 2 illustrate, on a more comprehensive scale, this phenomenon for males and females. The dominating position of England, Wales and Scotland for males and females in the international lung cancer pattern is particularly noteworthy as are the shifts in the relative position of the individual countries through the two decades surveyed within the scale.

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Fig. 2 presents the marked and, in part, at present unexplainable variation in lung cancer frequency in the different States of the United States.

Fig. 3 demonstrates the existence of similar regional differences in lung cancer death rates for England and Wales, where the highest rates are present in the highly industrialized areas of Greater London and the Midlands.

Fig. 4 displays a similar pattern of distribution of lung cancer death rates for Belgium where the heavily industrialized area of Liege has the highest lung cancer death rate, which contrasts sharply with the considerably lower one in the rural regions.

Table 3 exemplifies the existence of this general principle for the United States by showing the remarkable fluctuations in lung cancer death rates between metropolitan counties and rural counties in Ohio.

Table 4 demonstrates the presence of similar correlations for a number of communities of different size and population density in England. The lung cancer death rates decrease here with the relative size of the community.

Table 5. Similar correlations were reported by Prindle to prevail for groups of American cities of different size.

Table 6 illustrates another characteristic and important feature in the epidemiology of lung cancers which doubtlessly has significant etiologic implications. The table demonstrates the remarkable differences in lung cancer morbidity rates in different metropolitan cities of the United States and the definite fluctuations in the progression rates of lung cancer morbidity in these communities observed during a decade.

Table 7. Equally remarkable variations in lung cancer death rates were found by Manos when he analyzed cancer death rates in 163 American metropolitan areas.

Table 8. The doubtlessly etiologically important observation of epidemiologic irregularity becomes again apparent in the data listed in table 8, which shows that lung cancer death rates vary considerably among communities of similar size, suggesting thereby that definite variations in the quantitative and qualitative composition of the environmental respiratory carcinogenic spectrum seem to exist for different cities which may account for such fluctuations in lung cancer death rates of communities of similar size.

Figures 5 and 6. The apparent operation of such factors in determining local lung cancer rates is suggested, moreover, by the demonstration of definite differences even within several quarters of the same metropolitan area. The highest lung cancer death rates in London, as well as in Pittsburgh, were observed in the central business and industrial portions of these communities, where presumably the most severe degree of air pollution prevails.

Table 1

Frequency of Deaths from Lung Cancer in Different Countries

Rates per 100,000 Males

P. Kotin

| Country | Year and Death Rates of Lung Cancers | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Year | Rate | Year | Rate | Year | Rate | Year | Rate |
| England and Wales | 1930-32 | 12.9 | 1949 | 49.5 | 1952 | 61.4 | 1953 | 65.4 |
| Scotland | | 10.6 | | 41.4 | | 56.3 | | |
| Finland | 1936-38 | 13.6 | | 29.8 | | 38.0 | | 46.9 |
| Switzerland | 1929-31 | 12.0 | | 26.1 | | 33.5 | | 36.7 |
| Germany | | | | | | | | 33.1 |
| New Zealand | 1930-32 | 7.1 | | 21.6 | | 31.5 | | |
| Netherlands | 1929-31 | 7.2 | | 24.5 | | 30.3 | | 31.9 |
| France | | | | 21.7 | | 28.2 | | |
| United States | 1929-31 | 4.3 | | 21.5 | | 26.1 | | 28.3 |
| Denmark | 1934-36 | 4.5 | | 16.7 | | 24.8 | | |
| Ireland | 1935-37 | 5.4 | | 15.1 | | 22.2 | | |
| Australia | 1932-34 | 6.3 | | 16.7 | | 20.8 | | |
| Canada | 1930-32 | 4.2 | | 16.4 | | 19.0 | | |
| Austria | | | | | | | | 56.9 |
| Italy | 1931 | 3.0 | | 11.3 | | 16.4 | | |
| Norway | 1929-31 | 1.8 | | 9.0 | | 11.5 | | |
| Japan | | | | 3.3 | | 4.9 | | |

Table 2

Frequency of Deaths from Lung Cancer in Different Countries

Rates per 100,000 Females

P. Kotin

| Country | Year and Death Rates of Lung Cancers | | | | | | | | Position | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Year | Rate | Year | Rate | Year | Rate | Year | Rate | 1952 | 1930 |
| England & Wales | 1930-32 | 4.3 | 1949 | 9.8 | 1952 | 11.3 | 1953 | 11.8 | 1 | 2 |
| Scotland | | 5.6 | | 10.8 | | 10.9 | | | 2 | 1 |
| Finland | 1936-38 | 2.3 | | 5.4 | | 6.5 | | 5.3 | 4 | 6 |
| Switzerland | 1929-31 | 2.0 | | 4.7 | | 4.7 | | 5.4 | 10 | 9 |
| New Zealand | 1930-32 | 2.5 | | 3.9 | | 5.1 | | | 9 | 4 |
| Netherlands | 1929-31 | 2.2 | | 4.4 | | 4.0 | | 4.8 | 13 | 8 |
| Germany | | | | | | | | 6.3 | | |
| France | | | | 5.6 | | 6.1 | | | 6 | |
| United States | 1929-31 | 1.9 | | 4.9 | | 5.4 | | 5.11 | 7 | 11 |
| Denmark | 1934-36 | 2.5 | | 4.3 | | 6.2 | | 4.8 | 5 | 5 |
| Ireland | 1935-37 | 3.2 | | 4.5 | | 7.3 | | | 3 | 3 |
| Australia | 1932-34 | 2.3 | | 3.6 | | 4.3 | | | 12 | 7 |
| Canada | 1930-32 | 2.0 | | 4.6 | | 4.0 | | | 14 | 10 |
| Italy | 1931 | 1.4 | | 3.4 | | 4.5 | | 9.0 | | |
| Norway | 1929-31 | 1.2 | | 3.6 | | 5.4 | | | 8 | 13 |
| Japan | | | | 1.2 | | 2.2 | | | 15 | |
| Israel | | | | | | | | 10.8 | | |

Table 3

Standardized Mortality Rates for Lung Cancer in Urban and Rural Counties in Ohio for White Males, 25 - 64 Years Old

1947 - 1951

(Th. Mancuso)

| Type of County | Rate of Lung Cancer |
|---|---|
| 9 Metropolitan Counties | 122.9 |
| 7 Counties with Medium-Sized Cities | 81.9 |
| Rural Counties | 68.6 |

## Table 4

Relation of Density of Population in Urban Areas to Lung Cancer Rates 1946-1949
(P. Stocks)

| | Mortality Rate |
|---|---|
| Groups of Conurbations with More Than 200,000 Inhabited Houses: | |
| (London, East Ham, West Ham, Croydon; | 156 |
| Birmingham, Smethwick, Walsall, West Bromwich; | 134 |
| Liverpool, Bootle, Birkenhead, Wallasey; | 164 |
| Manchester, Salford, Stockport; | 159 |
| Leeds, Bradford, Halifax) | 132 |
| Sheffield with 124,000 Inhabited Houses | 135 |
| Newcastle and Gateshead with 87,000 Inhabited Houses | 114 |
| Groups of Cities each with 50,000 to 85,000 Inhabited Houses | 113 |
| Groups of 3 cities each with 40,000 to 50,000 Inhabited Houses | 107 |
| Groups of 12 cities each with 30,000 to 40,000 Inhabited Houses | 104 |
| Groups of 13 cities each with 20,000 to 30,000 Inhabited Houses | 100 |
| Groups of 29 cities each with less than 20,000 Inhabited Houses | 89 |

Table 5

Mortality Rates of Cancer of the Trachea, Bronchus and Lung for White Males and Percentage of Habitual Male Cigarette Smokers in Different Regions

(R. A. PRINDLE)

| Type of Region | Death Rate for 100,000 Inhabitants | Percentage of Habitual Cigarette Smokers |
|---|---|---|
| Cities with more than 1,000,000 Inhabitants | 25.4 | 48.5 |
| Urban Areas with 250,000 - 1,000,000 Inhabitants | 22.9 | 49.5 |
| Urban Areas with less than 250,000 Inhabitants | 17.5 | 47.8 |
| Rural Areas | 14.6 | 42.5 |

Table 6

Incidence of respiratory cancer, morbidity rates per 100,000 population for 9 metropolitan centers by sex, 1937 and 1947

| Primary site and city | Morbidity rates | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Males | | | Females | | | Total | | |
| | 1937 | 1947 | Percent increase | 1937 | 1947 | Percent increase | 1937 | 1947 | Percent increase |
| Bronchus and lung: | | | | | | | | | |
| Atlanta | 5.0 | 13.4 | 168 | 1.0 | 5.0 | 400 | 2.9 | 8.9 | 207 |
| New Orleans | 13.1 | 39.1 | 198 | 2.8 | 4.2 | 50 | 7.6 | 20.8 | 174 |
| Dallas | 5.9 | 29.0 | 392 | .5 | 6.4 | 1,180 | 3.1 | 17.2 | 455 |
| Birmingham | 4.5 | 18.9 | 320 | 2.1 | 3.9 | 86 | 3.3 | 11.0 | 233 |
| Denver | 9.1 | 21.9 | 141 | 4.2 | 8.1 | 93 | 6.6 | 14.8 | 124 |
| San Francisco | 15.6 | 34.3 | 120 | 3.9 | 8.1 | 108 | 9.6 | 20.8 | 112 |
| Chicago | 13.3 | 29.5 | 122 | 4.3 | 7.0 | 63 | 8.8 | 18.0 | 105 |
| Pittsburgh | 9.7 | 26.1 | 169 | 4.9 | 5.5 | 12 | 7.3 | 15.6 | 114 |
| Detroit | 12.6 | 32.0 | 154 | 2.3 | 5.7 | 148 | 7.6 | 19.0 | 150 |

Table 7

Ratio of Primary Lung Cancer Death Rates Standardized for

Age Distribution in 163 Metropolitan Areas to Rates for Entire United States

1949-1951 (Males)
(N. E. Manos)

| Low Ratios | | High Ratios | |
|---|---|---|---|
| Green Bay, Wisconsin | 0.2 | Birmingham, Alabama | 2.9 |
| Lima, Ohio | 0.3 | Mobile, Alabama | 2.8 |
| Pittsfield, Massachusetts | 0.3 | Columbus, Georgia | 2.5 |
| Springfield, Missouri | 0.4 | Montgomery, Alabama | 2.4 |
| Wichita Falls, Texas | 0.5 | Durham, North Carolina | 2.2 |
| Madison, Wisconsin | 0.5 | Winston-Salem, North Carolina | 2.1 |
| Brockton, Massachusetts | 0.5 | Kansas City, Missouri | 2.1 |
| Utica-Rome, New York | 0.5 | Buffalo, New York | 2.1 |
| Fall River, Massachusetts | 0.5 | Columbia, South Carolina | 2.0 |
| Worcester, Massachusetts | 0.5 | Rochester, New York | 2.0 |

Table

Lung Cancer Mortality Rate for Metropolitan Areas of Different Numbers of Inhabitants

| Metropolitan Areas Having Inhabitants From: | | | | | | | |
|---|---|---|---|---|---|---|---|
| 1,000,000 to 9,500,000 | | 500,000 to 1,000,000 | | 100,000 to 500,000 | | 50,000 to 100,000 | |
| Low Ratio: | | | | | | | |
| Boston | 0.8 | Worcester | 0.5 | Pittsfield | 0.3 | Green Bay | 0.2 |
| Pittsburgh | 0.9 | New Haven | 0.8 | Charlotte | 0.3 | Lima | 0.3 |
| High Ratio: | | | | | | | |
| Buffalo | 2.1 | Birmingham | 2.9 | Mobile | 2.8 | Pueblo | 1.7 |
| Washington, D. C. | 1.7 | Kansas City | 2.1 | Columbia | 2.5 | Amarillo | 1.7 |
| Los Angeles | 1.6 | | | | | | |

Fig. 1

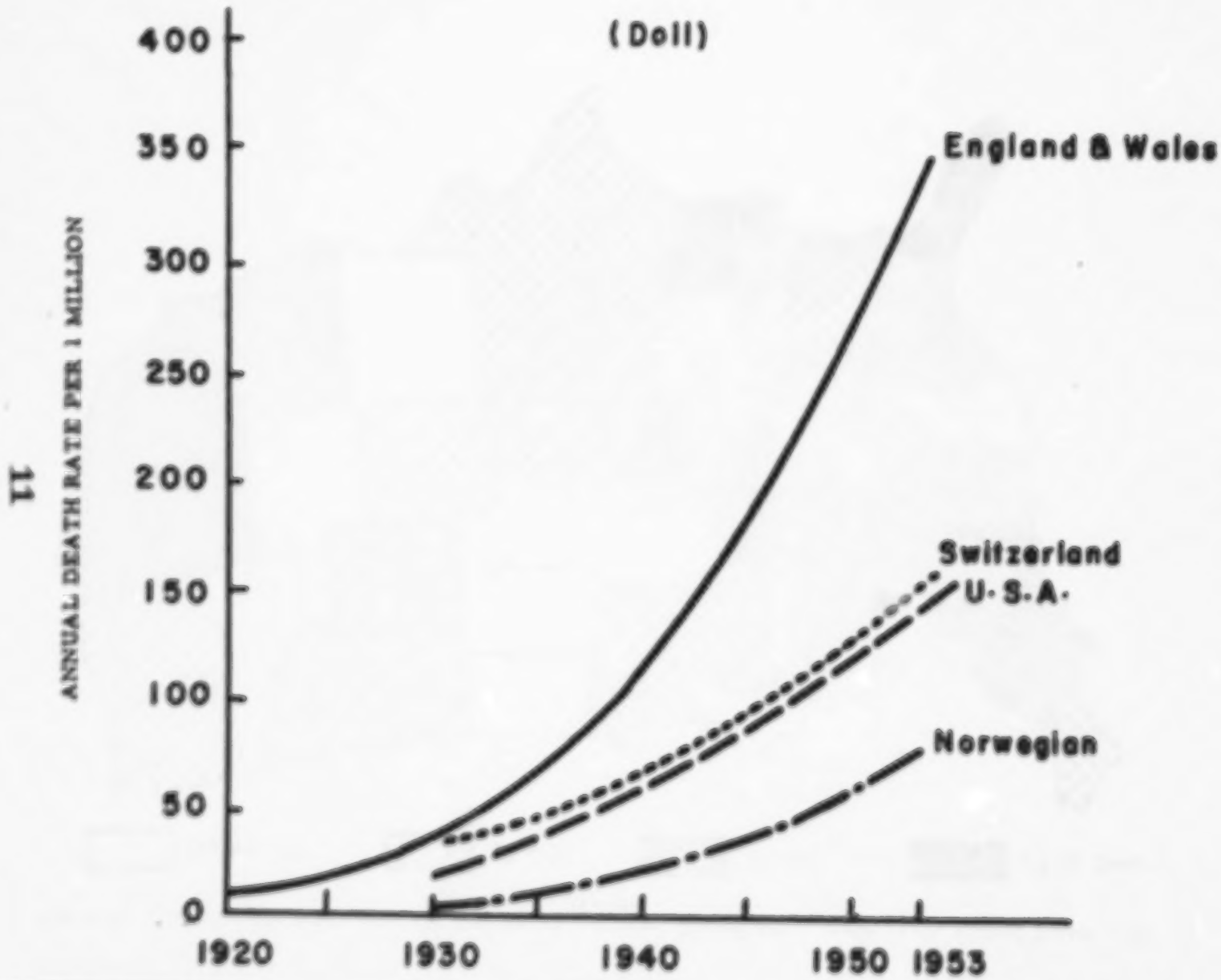
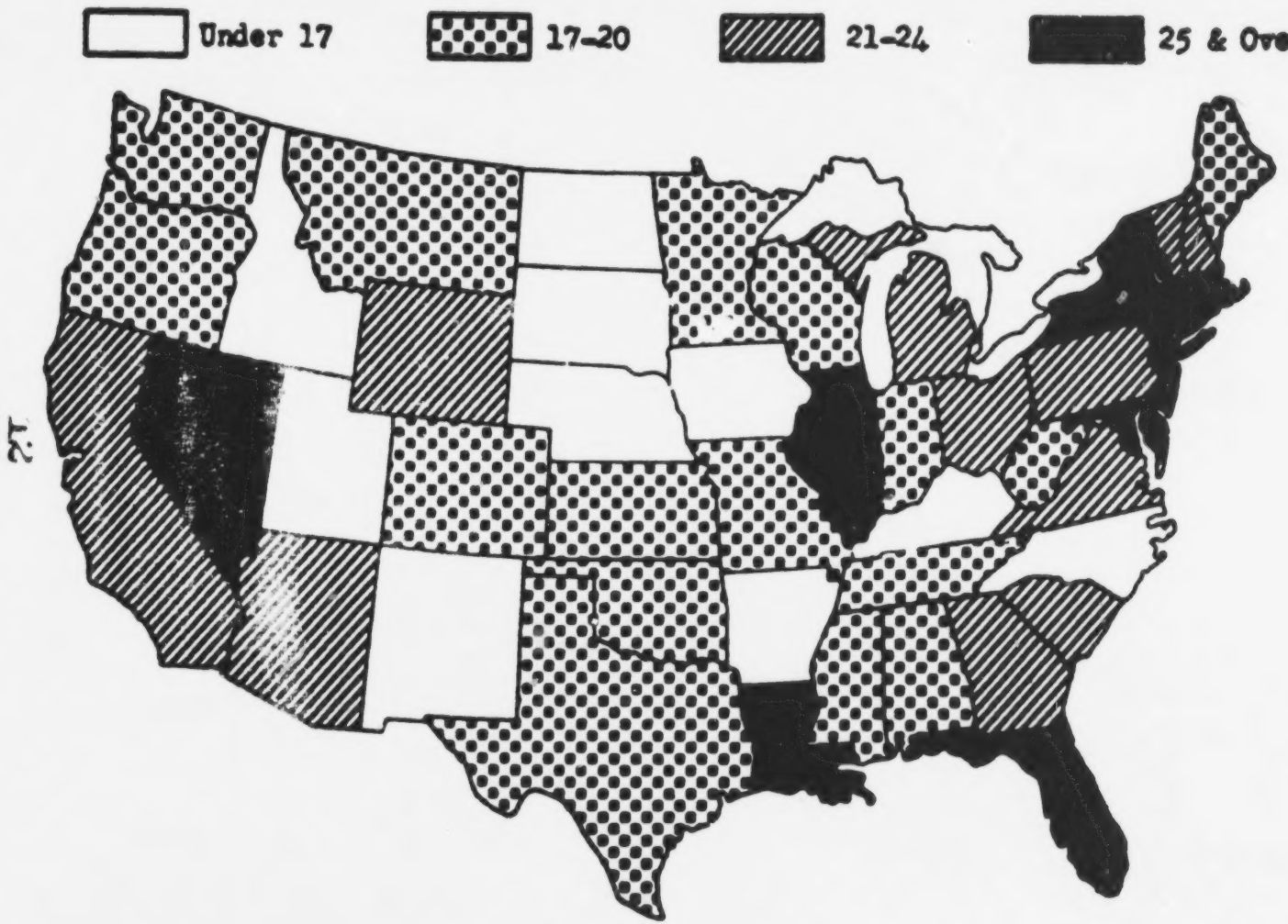

(Doll)
ANNUAL DEATH RATE PER 1 MILLION
11
400
350
300
250
200
150
100
50
0
1920
1930
1940
1950
1953
England & Wales
Switzerland
U.S.A.
Norwegian

**Figure 2.** Age-adjusted death rates for respiratory cancer per 100,000 white males in the United States, 1950. (Lew)



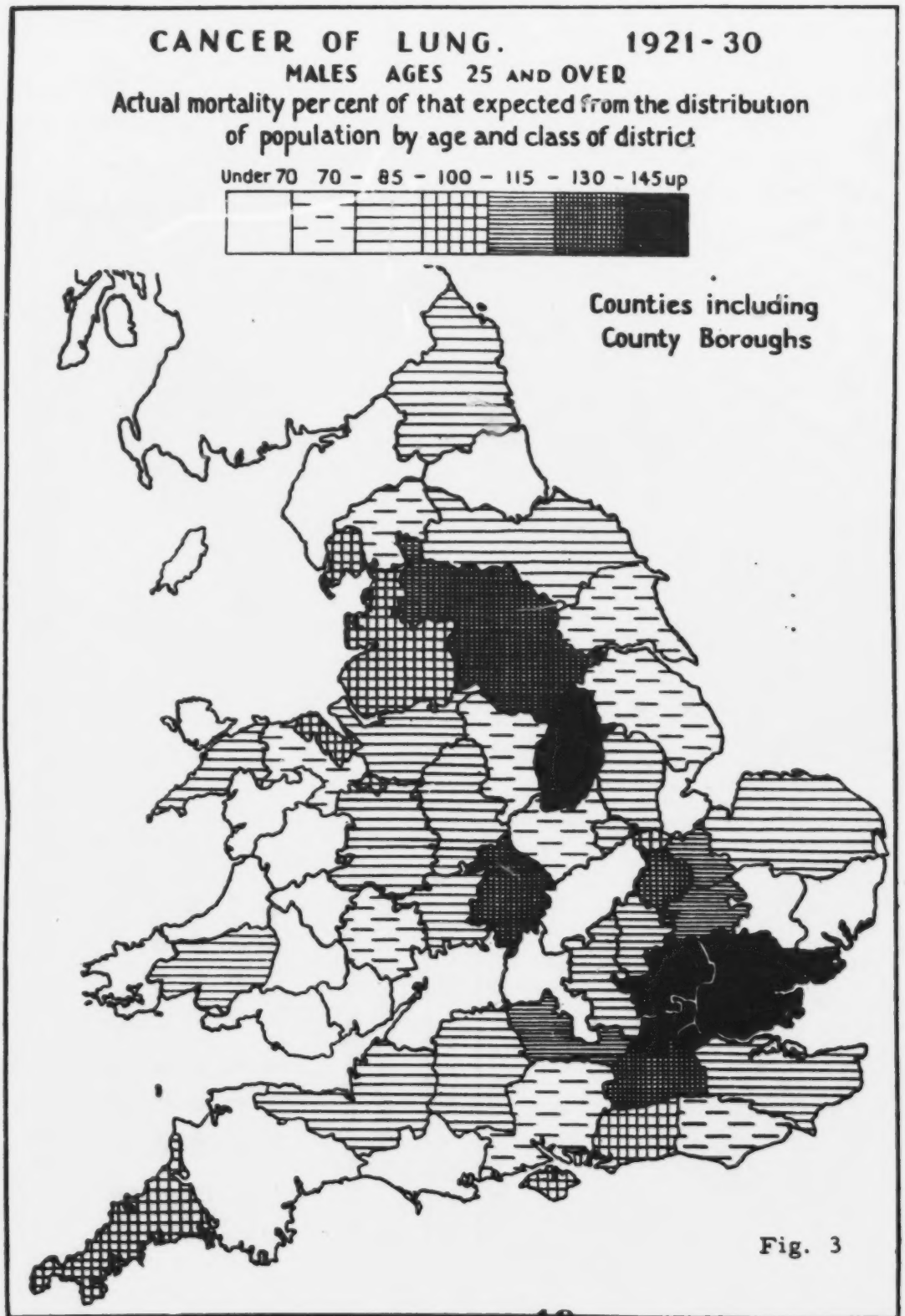

CANCER OF LUNG. 1921-30
MALES AGES 25 AND OVER
Actual mortality per cent of that expected from the distribution of population by age and class of district
Under 70
70 - 85 - 100 - 115 - 130 - 145 up
Counties including County Boroughs

Fig. 3

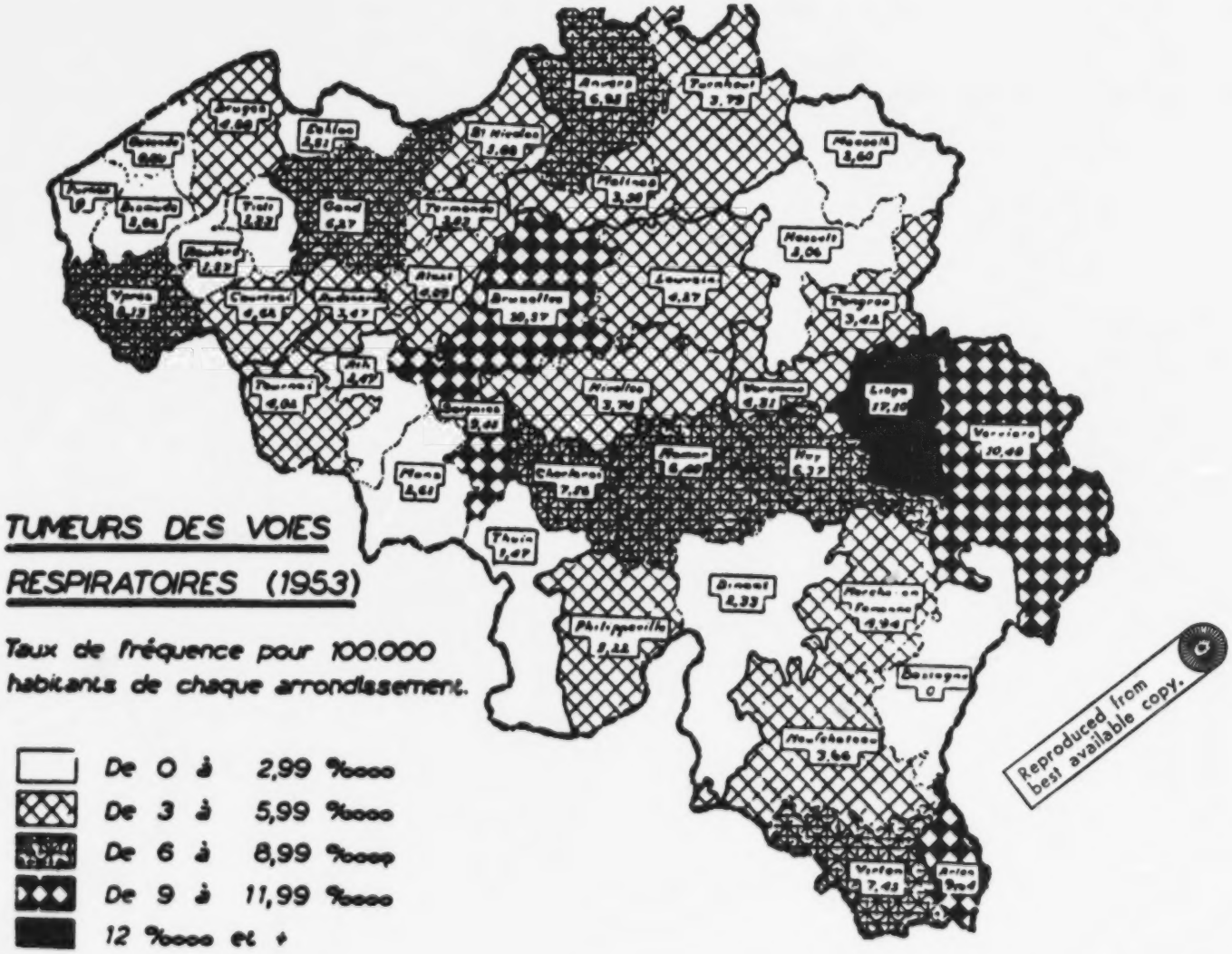

TUMEURS DES VOIES
RESPIRATOIRES (1953)
Taux de fréquence pour 100.000
habitants de chaque arrondissement.
De 0 à 2,99 ‰
De 3 à 5,99 ‰
De 6 à 8,99 ‰
De 9 à 11,99 ‰
12 ‰ et +
Reproduced from best available copy.

FIG. 4 —Map of Belgium giving the primary lung cancer in the different districts.

*Reproduced from Tuyns (1954) by kind permission.*

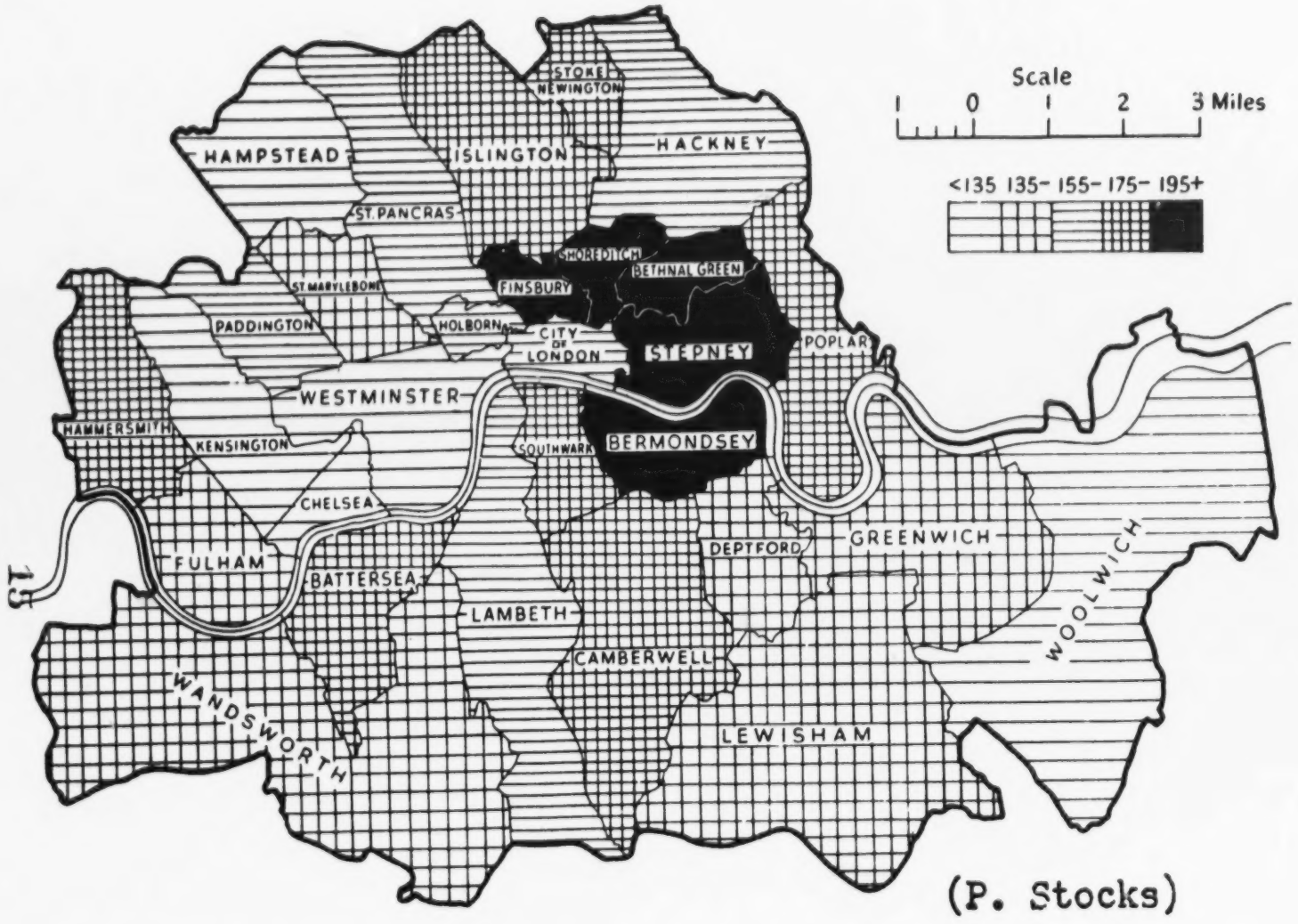
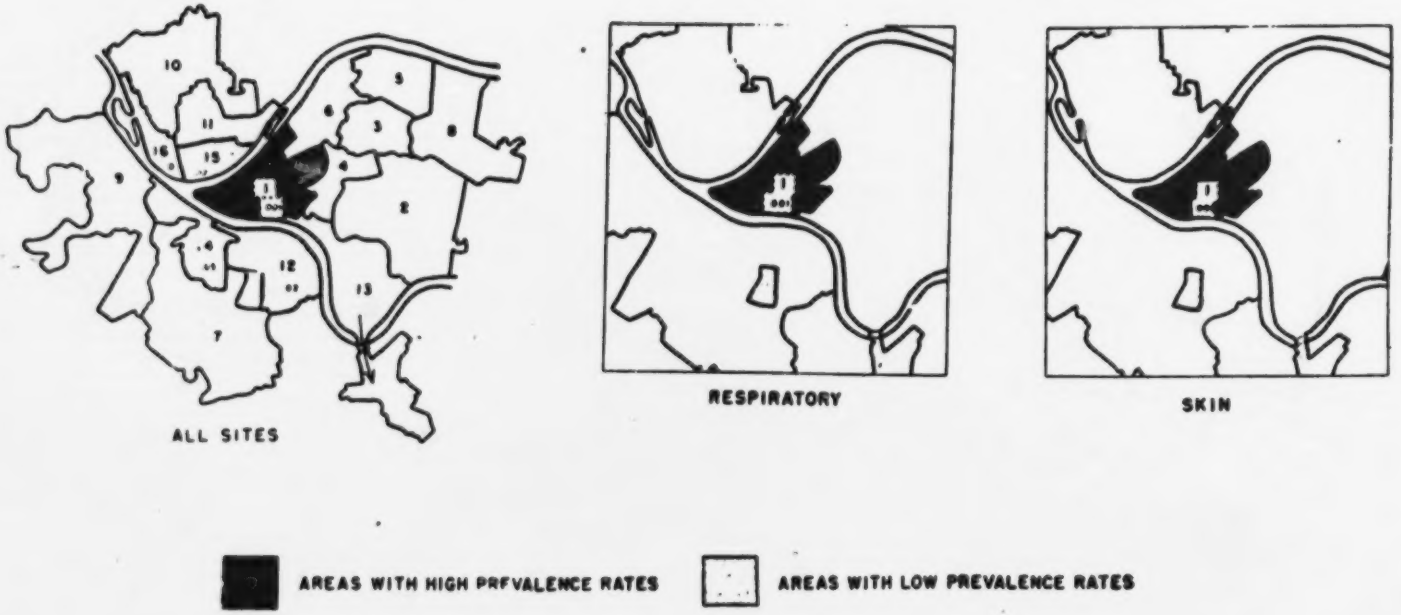



FIG. 5 —Cancer of lung, bronchus, pleura. 1946–49 deaths of males per 100 (calculated by applying rates for England and Wales to populations at ages 0–, 35–, 45–, 55–, 65–, 75–+) in the City of London and metropolitan boroughs.

Figure 6.
(Patno)

**Prevalence of cancer among white men and women, by site, in 16 areas of Pittsburgh, 1947.**

**White men.**



A. J. Phillips

FIG. 7

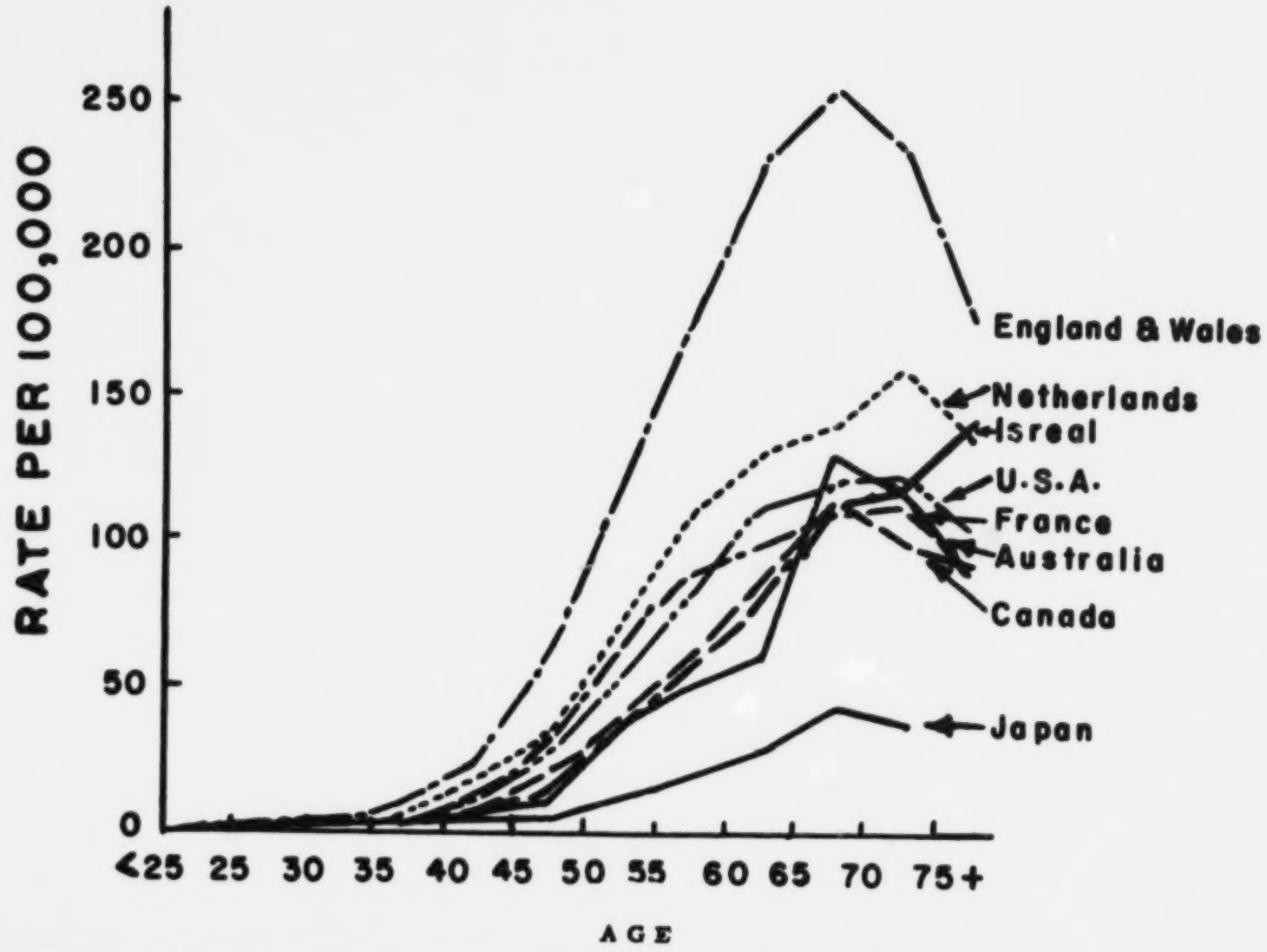


Fig. 7. A recent statistical analysis of Phillips concerning the age distribution of lung cancers in different countries also provides evidence concerning the remarkable regional irregularities of the lung cancer pattern. Phillips demonstrated that the age peak of lung cancers occurred by about one decade earlier among the inhabitants of England and Wales than among the populations of other countries. Such a shift in age distribution either can be attributed to a more intense action of a carcinogen or carcinogens often starting also at an earlier age in one population than in another population, or it may be due to the presence and the action of a carcinogen present in only one area but not in others.

When in the early 1920's, European pathologists noted in their autopsy material the first evidence of the rise in lung cancer frequency, various environmental agents were incriminated as being possibly responsible for this phenomenon. It is noteworthy that these factors which are listed in table 9 are still under consideration concerning their absolute and relative etiologic significance. The only group of at present recognized respiratory carcinogens which is absent from this list is composed of the occupational carcinogens because they had not been discovered, with the exception of the radiation lung cancers among the Schneeberg miners, first described in 1879. Among the various agents incriminated, two have come to the forefront during recent years as being allegedly of major importance in the causation and in the increase of lung cancers. These two agents are industrial and industry-related air pollutants and cigarette smoking.

Indeed, the definite discrepancies in the lung cancer rates for different countries, states, provinces and cities, which were presented in the tables shown, pointed to the action of local factors related to the scope, type and density of industrial activities and traffic conditions.

Additional specific data relative to such association support this concept. The evidence presented in tables 10 and 11, in fact, suggests the existence of such associations between general and occupational air pollution of specific industries and local lung cancer rates for areas in Connecticut and Montana. Chemical data on air pollutants also favor this view. The demonstration of considerable variations in the content of polycyclic aromatic hydrocarbons isolated from the particulate phase of air pollutants of many American cities and in their 3.4 benzpyrene content of both American and English cities provide this evidence (tables 12 and 13). It is remarkable, moreover, that the relative level of the 3.4-benzpyrene content of air pollutants in a number of English cities exhibited a rough, while not always consistent, parallelism with the lung cancer death rates found for these communities (table 14).

Recent epidemiologic studies on the relative lung cancer frequency among native white New Zealanders and English immigrants to New Zealand by Eastcott, among native white South Africans and English immigrants to South Africa by Dean, and among native white Americans and English and Italian

immigrants in Cleveland, Ohio, by Mancuso, have shown that English immigrants to the little industrialized New Zealand and South Africa have a distinctly higher lung cancer rate than the native whites of these two countries. This difference is also present, while to a lesser degree, for the native whites and British immigrants into highly industrialized Cleveland with a lung cancer rate (1.3) (tables 15, 15a and 16) rather high for American but not for English industrial cities.

The total evidence on hand doubtlessly supports the view that general air pollutants of industrial and industry related origin played a definite role in the causation and rise in frequency of lung cancers during recent decades. The data, moreover, make it likely that these air pollution factors may vary in quantity and quality in different regions and communities, thereby accounting for at least a considerable part of the observed fluctuations in lung cancer incidence among their inhabitants. It is also apparent from the information on hand that an effective and rational future control of lung cancer hazards from such sources definitely depends on the availability of a greatly increased and more specific knowledge of the nature, quantity, physical status and exposure mechanism of specific carcinogenic factors and on the presence and action of any associated promoting or cocarcinogenic and anticarcinogenic pollutants or climatic conditions present in a particular community.

Experimental Procedures and Results:

For obtaining this urgently needed information, a joint study of mainly exploratory and methodologic nature was organized in which the Environmental Cancer Section of the National Cancer Institute, the Air Pollution Medical Program, PHS, the Robert A. Taft Sanitary Engineering Center, PHS, and the Department of Pathology, University of Southern California, participated. The immediate aim of this preliminary investigation was directed at ascertaining the role which the quantity and quality of four solvent fractions of the particulate phase of air pollutants of eight specially selected metropolitan areas, their benzpyrene content, and the degree of carcinogenic potency of the four fractions, as reflected by the results of bioassays on mice, might assume in determining the lung cancer rates among the inhabitants of these communities. It was hoped that the outcome of these experiments might provide a rational basis for extending future, more comprehensive studies, perhaps in a modified and more specific form, if necessary, to other cities and other pollutants, such as minerals, radioactive matter, and gaseous constituents.

The present report had to remain of preliminary nature because only a few tentative data on the results of tests on the aliphatic and oxygenated fractions of the air pollutants were available when this communication was prepared. The complete results of these tests and their interpretation in the framework of this presentation, however, will be included in the final report on the first phase of carcinogenic studies on air pollutants obtained from American cities as a part of the studies carried out by the Air Pollution Program, U.S.P.H.S.

Table 9

Environmental Factors Suspect as Causes for Increased Frequency of Lung Cancers, 1900-1920

(Hueper, 1923)

1. Changes in Walls of Tuberculous Cavities and Syphilitic Scars in Lung.
2. Reactions in the Bronchial Mucosa Elicited by Influenza.
3. Frequent Administration of X-rays for Diagnosis and Therapy of Lung Diseases.
4. Smoking of Cigarettes.
5. Smoke and Dust of Cities.
6. War Gas Poisoning.
7. Dust of Tarred and Oiled Roads and Exhaust Gases of Automobiles.

Table 10

Lung Cancer Death Rates in 3 Districts of Connecticut

(Griswold)

| District | Occupational Character | Standard Lung Cancer Rates | | |
|---|---|---|---|---|
| | | Males | Females | Both |
| Naugatuck Valley Area | Rubber, Metal Machinery Chemical | 85.02 | 14.87 | 48.01 |
| Northeast Area | Textile Paper Agriculture | 69.24 | 21.69 | 45.01 |
| Rural | Agriculture | 30.60 | - | 15.00 |
| | Industry | 85.02 | 17.35 | 50.54 |
| | Agriculture | 38.65 | 14.87 | 26.53 |

Table II

Lung Cancer Mortality in Several Counties of Montana
1947-1948 (Lull and Wallach)

| County and Total Population 1940 | Major Industry | Numbers Lung Cancers | | | Total Cancer Deaths | Percent Lung Cancer | | Annual Lung Cancer Death Rate per 100,000 | |
|---|---|---|---|---|---|---|---|---|---|
| | | Male | Female | Total | | Male | Female | Male | Female |
| Deer Lodge | Copper | 21 | 0 | 21 | 98 | 30.8 | 0.0 | 145.7 | 0 |
| 13,627 | Smelting | -- | -- | -- | -- | -- | -- | -- | -- |
| Silver Bow | Copper | 27 | 2 | 29 | 259 | 22.6 | 1.5 | 48.6 | 3.9 |
| 53,207 | Mining | -- | -- | -- | -- | -- | -- | -- | -- |
| Cascade | Copper | 20 | 5 | 25 | 299 | 12.7 | 3.5 | 46.3 | 12.3 |
| 41,499 | Mining | -- | -- | -- | -- | -- | -- | --- | -- |
| | Smelting | -- | -- | -- | -- | -- | -- | --- | -- |
| Gallatin | Agriculture | 1 | 0 | 1 | 81 | 3.0 | 0.0 | 5.2 | 0 |
| 18,269 | | -- | -- | -- | -- | --- | -- | --- | -- |

The estimated crude death rate for lung cancer among white males in the entire United States in 1947 is 10.9 per 100,000 population.

The workers employed in copper ore mining and smelting inhale dust and fumes of arsenic contained in the ore and released as a by- and waste-product during the smelting process.

Table 12

Polycyclic Hydrocarbons in Particulate Phase of Air Pollutants
of American Cities and Their Lung Cancer Rates
L. A. Chambers, E. C. Tabor and M. J. Foter and N. E. Manos

| City | Lung Cancer Rate | Microgram/cbm Air |
|---|---|---|
| Atlanta | 1.6 | 4.2 |
| Boston | 0.8 | 5.9 |
| Charleston, W. Va. | 1.2 | 6.5 - 8.5 |
| Chattanooga | 0.6 | 1.2 - 4.7 |
| Chicago | 1.4 | 11.4 -29.6 |
| Cincinnati | 1.5 | 2.0 -10.1 |
| Fort Worth | 0.8 | 1.9 |
| Houston | 1.0 | 0.8 - 1.43 |
| Los Angeles | 1.8 | 2.55 - 4.95 |
| Louisville | 1.0 | 5.7 |
| Minneapolis | 1.1 | 2.1 |
| New Orleans | 1.9 | 1.23 |
| New York | 1.5 | 1.28 - 2.7 |
| Philadelphia | 1.5 | 1.21 - 4.04 |
| Portland | 1.4 | 0.59 |
| Providence | 0.9 | 1.4 |
| Salt Lake City | 1.0 | 3.0 |
| San Francisco | 1.4 | 0.29 - 5.25 |

Table 13

3.4-Benzpyrene Content in the Particulate Phase of Air Pollutants of English Cities

R. E. Waller

| City | Median Annual Concentration of 3.4-Benzpyrene in mcgm/100 cbm. Air | Smog Days |
|---|---|---|
| London | 4.6 | |
| Sheffield | 4.2 | 17.3 |
| Leicester | 2.9 | |
| Burnley | 2.7 | |
| Bilston | 2.7 | |
| Cannock | 1.9 | |
| Hull | 1.3 | |
| Bristol | 1.3 | |

Table 14

**Lung Cancer Death Rates and Content of Air of 3, 4-Benzpyrene In Communities near Liverpool**

**P. Stocks**

| Community | Type | Benzpyrene content in Microgram per 100 cbm Air | Standardized Lung Cancer Death Rate 1950-54 Expected Rate-100 |
|---|---|---|---|
| Conway Valley | Village | 0.1 | 59 |
| Llangefni | Village | 0.3 | 53 |
| Ruthin | Small Town | 0.5 | 15 |
| Blaenau | Town | 0.7 | 62 |
| Flint | Industrial Town | 1.85 | 74 |
| Ormskirk | Industrial Town | 2.2 | 95 |
| Hoylake | Resort City | 0.3 | 98 |
| Wrexham | Industrial Town | 1.95 | 78 |
| Chester | Industrial Town | 1.45 | 112 |
| Bootle | Suburb- Liverpool | 3.75 | 146 |
| Warrington | Industrial Town | 4.4 | 115 |
| St. Helens | Industrial Town | 4.75 | 111 |
| Birkenhead | Harbor Town | 3.3 | 132 |
| Liverpool | Harbor and Industrial Town | 2.95 - 6.75 | 158 |

Table 15

Observed and Expected Death Rate of Lung Cancer According to Place of Birth
New Zealand and Great Britain (D. F. Eastcott, 1956)

| Birthplace | Observed No. of Deaths | Expected No. of Deaths | Age at Time of Immigration from Great Britain | | | |
|---|---|---|---|---|---|---|
| | | | Observed | Expected | Observed | Expected |
| | | | Under 30 years of age | | Over 30 years of age | |
| New Zealand | 632 | 721.8 | --- | --- | --- | --- |
| Great Britain | 369 | 279.8 | 201 | 229.2 | 168 | 139.8 |

The excessive attack rate of English immigrants must be attributed to an exposure sustained before immigration and is probably due to industry-related air pollutants in Great Britain.

Table 15 a

Lung Cancer Death Rates Among White Males in South Africa, 1947-1956

per 100,000

G. Dean

| Country | Age Periods | |
|---|---|---|
| | 54-64 Years | 65+ Years |
| South Africa | | |
| Native Male Whites | 50 | 112 |
| British Immigrants | 112 | 172 |
| Others | 67 | 152 |
| England and Wales, 1951 | 135 | 219 |

Table 16

Death Rates of Lung Cancer in Male Immigrants, 25-64 Years of Age

Per 100,000 Population in Ohio

Th. F. Mancuso

| Population of: | Death Rate | Immigrants in Cuyahoga County from: | Death Rate |
|---|---|---|---|
| Cuyahoga County 1947-1951, Native White Americans | 28.75 | All Foreign Countries 1947 - 1951 | 38.11 |
| England and Wales, 1950 | 55.48 | England and Wales 1947 - 1951 | 31.75 |
| Italy, 1951 | 16.26 | Italy, 1947 - 1951 | 18.61 |

## Methods and Materials

Particulate air pollutants were collected on glass fiber filters at a height of not more than 20 feet above street level, where possible, in downtown and industrialized areas of the following 8 cities: New Orleans, Birmingham, Atlanta, Philadelphia, Detroit, Cincinnati, Los Angeles and San Francisco. These particular cities were selected for:

a) The availability of adequate epidemiologic data on morbidity and mortality rates from lung cancer among their inhabitants.

b) The existence of, in part, marked differences in these rates among the cities chosen.

c) The demonstration of considerable variations in the quantities of solvent soluble fractions of air pollutants in different cities.

d) The demonstration of distinct differences in the chemical composition of the organic fractions of the particulate phase of air pollutants in different cities, depending in part upon specific sources (industries, automobile traffic, coal or petroleum fuel economy).

Since the bioassay work was to be restricted to testing only organic fractions of the particulate phase of air pollutants for carcinogenic potency, the following four fractions were selected: Crude benzol soluble fraction, aromatic hydrocarbon fraction, aliphatic hydrocarbon fraction and oxygenated fraction. The fractions were prepared from composite collections made over one month, and therefore could be considered to be roughly representative of the atmospheric pollution prevailing in a particular city and at the particular sites during this period. The fractions were placed into glass ampoules in a nitrogen atmosphere and kept under refrigeration until used.

The fractions were washed from the ampoules with methylene chloride (spectra-analyzed grade). In order to obtain a uniform suspension, the proper amount (0.1 ml. for each individual dose of the material) of tricaprylin was added. The methylene chloride was then evaporated under vacuum at room temperature.

The filters used for the collection of the air pollutants were weighed before and after being used for determining the total amount of pollutants collected. They were then extracted with benzol. Through the evaporation of the benzol, the "crude benzol soluble fraction" was obtained, the weight of which was ascertained. A portion of this fraction was then used for obtaining the aromatic, aliphatic and oxygenated fractions (table 17). Bioassays for carcinogenic potency, according to a predetermined scheme,

were performed on the crude benzol soluble fraction and on the aromatic fraction at the National Cancer Institute, while those on the aliphatic and oxygenated fractions were done at the Department of Pathology, University of Southern California.

An attempt was made to administer standardized and equivalent amounts of the various fractions so as to obtain, if possible, comparable results. Taking into account the limited availability of the test materials and possible acute inflammatory and necrotizing effects, it was decided to use 4 mgs. of the benzol extract suspended in 0.1 ml. of tricaprylin (Eastman trioctanoin) as the individual dose to be given once a month into the subcutaneous tissue of the nape of the neck of C57 black mice. Since the amount of aromatic fraction obtained from a particular crude benzol soluble fraction varied with different cities and different batches, it was decided to use that amount of the aromatic fraction which could be extracted from 4 mgs. of the crude benzol soluble fraction at a given time and batch, as the monthly dose. This amount could be calculated, since the total weight of the crude benzol soluble fraction used for the isolation of the aromatic fraction was known for each batch as was the total yield by weight of this fraction (table 18).

The single dose of the crude benzol extract, as well as its equivalent of the aromatic fraction, was doubled after 11 months. This dosage was maintained until the end of the experiment.

For the testing of each fraction, a total of 72 C57 black mice, about 2 months old, equally divided as to sex, were used. The mice were kept in stainless steel shoebox cages. The cages were examined twice a day for dead animals. Mice which developed tumors at the site of injection were sacrificed when the tumors measured about 1 cm. in diameter. This scheme was adopted, since it seemed to be advisable to determine not only the tumor yield for each fraction, but also the approximate length of the latent period for judging the relative potency of the various fractions. Since it is difficult to determine the time of the actual beginning of a cancer, it was decided to use for this purpose rather the period at which a given tumor reaches a certain size. The maximal observation period was 2 years. At the end of it, the surviving animals were sacrificed.

Two series of mice, one receiving monthly 0.1 ml. of tricaprylin and the second being given 0.2 ml. of this vehicle, served as controls.

In parallel experiments, 50 strain C57 black mice received monthly subcutaneous injections of 0.5 mg. of the oxygenated fraction suspended in 0.2 ml. of tricaprylin which was administered into the nape of the neck. Because the aliphatic fraction was considered to be the least toxic and caustic, fraction 50 C57 black mice received monthly injections of 1 mg. of this fraction suspended in 0.2 ml. of tricaprylin.

Previous investigations of other investigators had demonstrated the presence of 3.4-benzpyrene in the particulate phase of urban air pollutants. The availability of similar information on the air pollutants to be tested

TABLE 17

CHART "I"

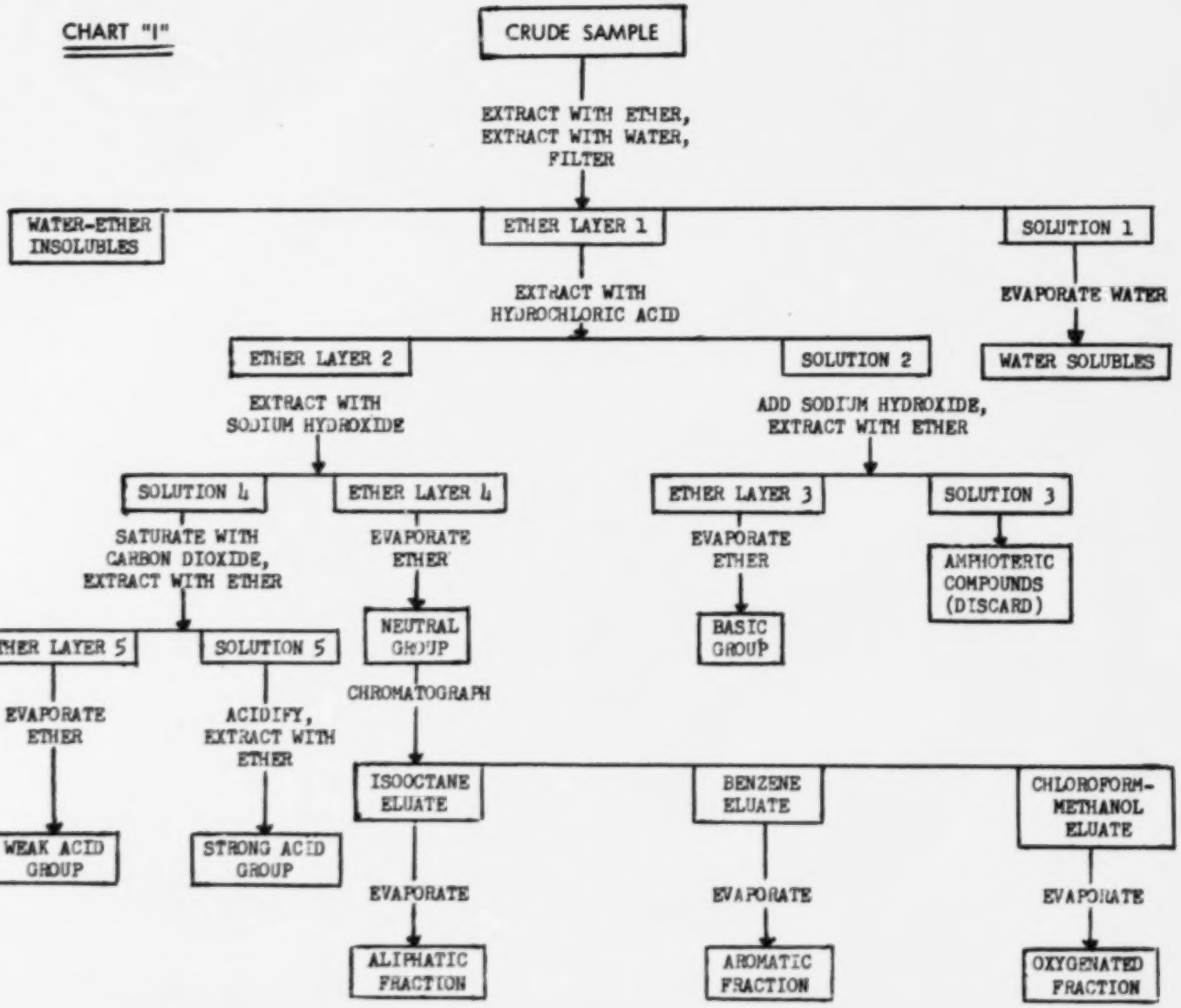


Table 18

Variations in the Relative Amounts of Aromatic Compounds in The Crude Benzol Soluble Fraction of Different Cities

| Cities | Crude Benzol Soluble Fraction | Aromatic Hydrocarbon Fraction |
|---|---|---|
| Atlanta | 0.300 gm. | 0.063 gm. |
| Birmingham | | 0.082 |
| Cincinnati | | 0.050 |
| Detroit | | 0.058 |
| Los Angeles | | 0.032 |
| New Orleans | | 0.037 |
| Philadelphia | | 0.068 |
| San Francisco | | 0.064 |

in the present study appeared indicated for attempting to determine whether or not a correlation existed between the degree of carcinogenic responses obtained with the various fractions and their relative 3.4-benzpyrene content. Because of the presence of numerous other chemicals in the various fractions, it was possible that the total carcinogenic effect elicited by a fraction not only could depend on its benzpyrene content, but also could be influenced in a positive or negative direction by other carcinogenic, cocarcinogenic or anticarcinogenic substances present in the fraction.

For this reason it was necessary to obtain a scale of cancerous responses to graduated doses of 3.4-benzpyrene given as a single dose as well as in 12 monthly fractionated doses (table 19) injected subcutaneously into the nape of the neck in C57 black mice, using sets of 72 mice for each dose. Through this scale it was hoped to obtain a method for possibly estimating the approximate share which could be attributed to 3.4-benzpyrene present in a particular fraction in the production of the total cancerous response observed. The scale appeared also to be suitable for expressing the total cancerous response to a particular fraction in terms of standardized doses of 3.4-benzpyrene.

The experimental scheme adopted seemed to permit thus the determination of the absolute and relative carcinogenic potency of various solvent fractions of the particulate phase of air pollutants collected in 8 metropolitan areas in the United States. It was likely that this methodologic approach might also yield some information on the relative share of carcinogenic potency which three subfractions (aromatic, aliphatic and oxygenated) contributed to the carcinogenic potency of the total fraction (crude benzol soluble), and whether or not the sum of the carcinogenic responses of the three subfractions would account for that of the total fraction. Finally, there was a possibility for ascertaining whether the 3.4-benzpyrene content of the crude benzol soluble fraction would account for the total carcinogenic response obtained from all fractions, or whether non-aromatic and non-benzpyrene constituents, or even non-organic chemicals, might contribute a significant share to the carcinogenic potency of air pollutants in different cities.

## Results

The results of the bioassays performed under the experimental conditions stated are summarized in table 20. The great majority of the cancers produced at the site of injection of the air pollutant fractions were spindle cell and fibrosarcomas. Only four of them were squamous cell carcinomas of the epidermis. The cancers observed in the mice which were located remote from the site of administration of the test material were with three exceptions lymphomas, leukemias and reticulum cell sarcomas. The exceptions were a hemangiosarcoma of the liver, an adenocarcinoma of the uterus, and a papillary adenocarcinoma of the lung in one of three mice.

The incidence rate of tumors remote from the site of injection was about the same among the mice of the tests series as that among the controls, indicating thereby that the air pollutant fractions had not stimulated the development of "spontaneous" cancers among the test animals. Since no cancers appeared in the nape of the neck of mice injected with the vehicle tricaprylin only, all cancers seen at this site in the test series must be attributed to carcinogenic effects exerted by the test materials injected. The total yield of cancers at the site of administration of the fractions stands at about 2% of the total number of animals used. If those animals are eliminated which died before the appearance of the first of these cancers, the tumor yield for the different fractions varies from 2% to 10%, and the minimal "latent period" from 9 - 18 months (table 21).

Although the number of cancers of this origin is relatively small, an analysis of the data recorded nevertheless reveals some interesting and probably significant discrepancies in the degrees of cancerous responses to the various air pollutant fractions of the same city as well as of different cities. The absent or lov cancer yield of the crude benzol and aromatic fractions of Los Angeles and New Orleans and the definite carcinogenic responses to the aliphatic fraction from these cities deserve attention and necessitate more comprehensive additional investigation from a chemical viewpoint concerning the original nature of air pollutants and the chemical changes which they may undergo because of special atmospheric and climatic conditions.

The high cancer rate produced by pollutant fractions of Birmingham is remarkable, since this community has, according to the data of Manos, the highest lung cancer rate among the 163 metropolitan communities analyzed. The total tumor yield of the air pollutant fractions of the other cities is at approximately the same plane. A comparison between the total cancer response to the crude benzol soluble fraction of the eight cities and the sum of the tumor responses to the three subfractions reveals that the latter is only moderately higher (20%) than the former (30 to 24). It is doubtful whether this difference is always significant considering the experimental conditions used in these bioassays. From the results obtained, it is rather likely that the crude benzol extract often contains the bulk of the carcinogenic materials in an available and active form and that any influence which any hypothetical cocarcinogenic or anticarcinogenic constituents of this fraction and the three subfractions upon the degree of tumor yield may have exerted is not readily apparent.

A noteworthy feature of the observations made is, moreover, presented when the tumor yield of the crude benzol extract and aromatic fractions containing the bulk of the 3.4-benzpyrene present in different cities (table 22) in the air pollutants is compared with the tumor yield of cancers seen after the subcutaneous injection of single or repeated graduated doses of 3.4-benzpyrene (table 23). The average content of

TABLE 19

SUBCUTANEOUS INJECTION OF BENZO(a)PYRENE
IN MICE IN SINGLE AND REPEATED MONTHLY DOSES

| NUMBER OF MONTHLY INJECTIONS | AMOUNT OF BENZ PYRENE PER MOUSE, MILLIGRAMS | |
|---|---|---|
| | PER INJECTION | TOTAL |
| 1 | (Controls) | (Controls) |
| 1 | 0.008 | 0.008 |
| 1 | 0.013 | 0.013 |
| 1 | 0.025 | 0.025 |
| 1 | 0.05 | 0.05 |
| 1 | 0.10 | 0.10 |
| 1 | 0.25 | 0.25 |
| 1 | 0.50 | 0.50 |
| 12 | (Controls) | (Controls) |
| 12 | 0.002 | 0.024 |
| 12 | 0.004 | 0.05 |
| 12 | 0.008 | 0.10 |
| 12 | 0.02 | 0.24 |
| 12 | 0.04 | 0.48 |

36 Male and 36 Female C-57 Black Mice per group.
Vehicle: 0.1 ml. Tricaprylin per injection.

Table 20

Cancers in Mice Receiving Repeated Subcutaneous Injections of Organic Solvent Fractions of the Particulate Phase of Air Pollutants of Eight American Cities

| Cities | Cancerous Reactions | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Benzol | | Aromatic | | Oxygenated | Aliphatic | Total | |
| | Site | Remote | Site | Remote | Site | | Site | Remote |
| Atlanta | 6 | 0 | 3 | 2 | 0 | 0 | 9 | 2 |
| New Orleans | 1 | 2 | 2 | 3 | 0 | 3 | 6 | 5 |
| Birmingham | 4 | 1 | 5 | 4 | 4 | 0 | 13 | 5 |
| Los Angeles | 0 | 1 | 0 | 2 | 2 | 2 | 4 | 3 |
| San Francisco | 3 | 1 | 1 | 2 | 1 | 0 | 5 | 3 |
| Cincinnati | 3 | 1 | 1 | 2 | 1 | 1 | 6 | 3 |
| Philadelphia | 3 | 4 | 0 | 1 | 2 | 0 | 5 | 5 |
| Detroit | 4 | 1 | 0 | 1 | 0 | 0 | 4 | 2 |
| Total | 24 | 11 | 12 | 17 | 10 | 6 | 52 | 28 |
| Total No. Mice | 864 | | 864 | | 600 | 600 | 2928 | 1728(1.5%) |
| Control Mice | 144 | | | | | | | 2 (1.4%) |

Table 21

Length of Latent Periods and Cancer Rates In Mice Injected With the Crude Benzol Soluble Fraction and Aromatic Hydrocarbon Fraction of Air Pollutants

| City | Fraction | Latent Period in Months | No. of Survivors | No. Cancers | Percentage of Cancers |
|---|---|---|---|---|---|
| Atlanta | Crude Benzol | 15 | 41 | 3 | 7 |
| | Aromatic | 12 | 55 | 4 | 7 |
| Birmingham | Crude Benzol | 9 | 66 | 5 | 8 |
| | Aromatic | 12 | 55 | 2 | 4 |
| New Orleans | Crude Benzol | 12 | 55 | 2 | 4 |
| | Aromatic | 12 | 57 | 5 | 9 |
| Los Angeles | Crude Benzol | | | 0 | |
| | Aromatic | | | 0 | |
| San Francisco | Crude Benzol | 12 | 55 | 3 | 5 |
| | Aromatic | 9 | 68 | 1 | 2 |
| Cincinnati | Crude Benzol | 12 | 55 | 3 | 5 |
| | Aromatic | 12 | 58 | 6 | 10 |
| Detroit | Crude Benzol | 15 | 35 | 2 | 6 |
| | Aromatic | | | 0 | |
| Philadelphia | Crude Benzol | 18 | 41 | 3 | 7 |
| | Aromatic | 12 | 62 | 1 | 2 |

Table 22

3,4-Benzpyrene Content of the Crude Benzol Extract of the Particulate Phase of Air Pollutants of Eight American Cities

3,4-Benzpyrene Content Expressed in Micrograms of Grams of Extract

| City | Lot 18 | Lot 19 | Lot 20 | Lot 21 | Lot 22 | Lot 23 | Lot 24 | Lot 25 | Lot 26 | Lot 27 | Lot 28 | Lot 29 | Range | Average | Median |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Atlanta | 270 | 620 | 897 | 422 | 558 | 532 | 620 | 544 | | | | | 270-897 | 558 | 551 |
| Birmingham | 840 | 809 | 816 | 940 | 1043 | 1412 | 1600 | 1340 | | | | | 809-1600 | 1100 | 991 |
| New Orleans | 340 | 277 | 264 | 240 | 264 | 399 | | 336 | | | | | 240-399 | 303 | 277 |
| Los Angeles | 26 | 44 | 39 | 44 | 90 | 84 | 70 | 178 | 113 | 119 | | | 26-178 | 81 | 77 |
| San Francisco | 110 | 143 | 118 | 205 | | 202 | 189 | 222 | | | | | 110-222 | 170 | 189 |
| Cincinnati | 278 | 770 | 989 | 972 | 1140 | 1490 | | | | | | | 278-1490 | 940 | 980 |
| Detroit | | 1130 | 1350 | 730 | 1032 | 973 | 1435 | 1580 | | | | | 730-1580 | 1176 | 1130 |
| Philadelphia | 310 | 450 | 682 | 541 | 320 | 389 | | | | | | | 310-682 | 449 | 420 |

TABLE 23

TUMORS IN MICE INJECTED WITH VARYING AMOUNTS OF BENZO (a) PYRENE IN SINGLE AND REPEATED MONTHLY DOSES

Number of Mice with Tumors at Site of Injection and and Number of Survivors after Specified Intervals

| Total Dose mg. | | Cumulative No. of Mice with Tumors and No. Survivors | | | | | | | | Per cent of Total Animals With Tumors at Site |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 3 mo. | 6 mo. | 9 mo. | 12 mo. | 15 mo. | 18 mo. | 21 mo. | 24 mo. | |
| Controls | Single | 0/69 | 0/68 | 0/63 | 0/39 | 0/16 | 0/6 | 0/5 | 0/0 | 0 |
| Controls | Monthly | 0/71 | 0/67 | 0/46 | 0/31 | 0/17 | 0/2 | 0/2 | 0/0 | 0 |
| 0.008 | Single | 0/71 | 0/70 | 0/67 | 0/54 | 0/37 | 0/18 | 0/9 | 0/0 | 0 |
| 0.013 | Monthly | 0/70 | 0/69 | 0/68 | 0/61 | 0/47 | 0/13 | 0/8 | 0/0 | 0 |
| 0.025 | Single | 0/71 | 1/68 | 6/62 | 6/50 | 7/30 | 7/12 | 7/7 | 7/0 | 10 |
| 0.024 | Monthly | 0/69 | 0/68 | 0/66 | 1/62 | 1/50 | 2/34 | 2/24 | 2/0 | 3 |
| 0.05 | Single | 0/72 | 3/68 | 5/65 | 7/47 | 7/31 | 7/31 | 7/5 | 7/0 | 10 |
| 0.05 | Monthly | 0/72 | 0/71 | 2/69 | 4/62 | 4/47 | 5/33 | 7/13 | 7/0 | 10 |
| 0.10 | Single | 0/71 | 17/53 | 17/53 | 17/48 | 17/36 | 17/20 | 17/15 | 17/0 | 24 |
| 0.10 | Monthly | 0/72 | 0/69 | 6/61 | 10/52 | 12/45 | 19/31 | 26/12 | 27/0 | 38 |
| 0.25 | Single | 0/70 | 12/55 | 18/49 | 20/46 | 20/36 | 20/22 | 20/13 | 20/0 | 28 |
| 0.24 | Monthly | 0/71 | 4/67 | 16/52 | 23/42 | 32/26 | 43/9 | 44/6 | 44/0 | 61 |
| 0.50 | Single | 0/71 | 14/56 | 18/52 | 19/43 | 19/23 | 19/19 | 19/12 | 19/0 | 26 |
| 0.48 | Monthly | 0/70 | 2/68 | 19/51 | 34/31 | 46/12 | 52/4 | 53/2 | 53/0 | 74 |

36 Male and 36 Female C-57 Black Mice in Each Group.

3.4-benzpyrene per 8 mgs. of crude benzol extract is about 9 micrograms. This amount approximates that used in the standard set given the smallest dose of 3.4-benzpyrene (8 micrograms), which showed a negative tumor yield. Four cancers, on the other hand, were obtained with the crude benzol extract of air pollutants of Birmingham. This discrepancy suggests that a definite part of the carcinogenic action of this fraction cannot be attributed to 3.4-benzpyrene, but must be due to other carcinogenic agents. This explanation received some support from the fact that the total cancer yield of the crude benzol fractions was twice that of the aromatic fraction. Although this fraction had a proportionally higher 3.4-benzpyrene concentration than the crude benzol fraction (table 24), the higher benzpyrene content of this fraction could not come into play, because equivalent doses of the aromatic fractions were used for maintaining comparable conditions of exposure.

If an analysis of the data obtained by bioassays and chemical investigations revealed the existence of rather complex conditions and of considerable variations between solvent fractions of urban air pollutants, which did not favor the demonstration of consistent associations between these factors and the lung cancer rates observed in individual cities involved, this suspicion was confirmed when an attempt was made to establish correlations between the following items: Total cancer yield of all four fractions, cancer yield by the crude benzol soluble fraction, benzpyrene content of the crude benzol fraction, equivalent benzpyrene cancer rate, (repeated injection), and city lung cancer rate (1949-1951) (table 25). With the single exception of the data related to Birmingham, for which positive associations were demonstrable, the data of no other city exhibited any significant associations. These findings, which differ considerably from those observed in England, suggest the presence of pollution conditions of much higher complexity in American cities than those apparently prevailing in England. It seems that the carcinogenic pollutant spectrum of urban areas in the United States exhibits a great measure of individuality which may vary significantly with the type of industrial activities, transportation facilities, climate, chief kind of fuel used and local meteorological and geologic conditions. The remarkable observation concerning the marked differences in the 3.4-benzpyrene content of the particulate phase of air pollutants of eastern and western American cities represents one illustration of such variations (Sawicki).

Comments

The present investigations confirm previously reported observations on the successful production of cancers in mice exposed to condensates of crude benzol extracts of the particular phase of urban air pollutants (Leiter and Shear; Kotin and Falk; and others) and on the demonstration of 3.4-benzpyrene in such materials reported by several English and American workers (Waller; Stocks and Campbell; Kotin and Falk). These studies provide also additional evidence indicating that solvent fractions apparently free from 3.4-benzpyrene, also possess carcinogenic properties to mice (Kotin and Falk). One of the new contributions of this exploratory methodologic approach to the problem of air pollutants and lung cancer hazards is represented by the demonstration of distinct variations in the quantitative and qualitative composition of air pollutants from different cities as reflected by the solvent fractions studied and by the observation of distinct discrepancies in the carcinogenic responses obtained by a repeated subcutaneous administration of standardized amounts of these fractions. If, therefore, the assumption is correct that these constituents of the total spectrum of atmospheric carcinogenic air pollutants are responsible for a still undetermined part of the lung cancers developing among urban populations, it is obvious that the share which any particular fraction has in such cancerous reactions most likely would vary in different cities and would depend on the degree to which the individual fractions contribute to the total air pollution.

It may be pertinent in this connection to discuss briefly the still not definitely answered question whether these aromatic and non-aromatic organic chemical carcinogenic materials are actually causally involved in the production of lung cancers in man, because they are present in the air in rather low concentrations. There can be no doubt that an occupational and more massive exposure to the same substances encountered by workers employed in the operation of coke ovens and gas retorts is the direct cause for the definitely elevated incidence of lung cancers found among such worker groups according to observations reported from England, Canada, Japan, Poland, and Norway (table 26). Slightly less certain is the evidence which incriminates an occupational inhalation of cutting and lubricating oil mists of carcinogenic semirefined paraffin oils as a cause of lung cancer among metallurgical workers, mechanics, paraffin pressers and members of similar occupations (Hueper).

The arguments which may be advanced in favor of a positive association between an exposure of carcinogenic aromatic and aliphatic air pollutants present in relatively low concentrations in the atmosphere and derived from an incomplete combustion of carbonaceous fuel, such as coal, oil and gasoline and from a release of oil fumes and gasoline vapors into the atmosphere mainly with the exhaust of gasoline and diesel motors, represent circumstantial evidence which, however, is of definitely incriminating significance. Experiences obtained from the study of occupational cancers and from determinations of the relative carcinogenic potency of various polycyclic aromatic hydrocarbons in experimental animals have definitely shown that a reduction in the dose of a carcinogen or of its concentration in the environmental medium is followed by a corresponding, although not proportional drop of the incidence rate of the cancerous responses among the

Table 24

3, 4-Benzpyrene Content of the Aromatic Hydrocarbon Fraction of Air Pollutants of Eight American Cities

| City | 3, 4-Benzpyrene Expressed in Micrograms per Gram of Aromatic Fraction | |
|---|---|---|
| | Lot 19 | Lot 20 |
| Atlanta | 1522 | 1537 |
| Birmingham | 1950 | 2834 |
| Cincinnati | 2362 | 4362 |
| Detroit | 3115 | 3776 |
| Los Angeles | 548 | 214 |
| Nashville | 4921 | 4115 |
| New Orleans | 1709 | 1323 |
| Philadelphia | 2045 | ? |
| San Francisco | 568 | 240 |

Table 25

**Correlations Between Total Cancer Yield, Crude Benzol Extract Cancer Yield, Benzpyrene Content of Crude Benzol Fraction, Length of Latent Period, Lung Cancer Rate of City and Standardized Benzpyrene Cancer Rate of Equivalent Dose**

| City | Total Cancer Yield at Site | Crude Benzol Cancer Yield at Site | Length of Latent Period Crude Benzol | Benzpyrene of Benzol Fraction | City Lung Cancer Rate 1949-1951 | Equivalent Bzp. Cancer Rate: Rep. |
|---|---|---|---|---|---|---|
| | | | | mcrg/g | | |
| Atlanta | 9 (12%) | 6 (8%) | 15 | 200 - 897<br>Av. 565 | 1.6 | 0.025-<br>0.05 mg. |
| Birmingham | 9 (12%) | 5 (7%) | 9 | 890 - 1600<br>Av. 1100 | 2.9 | 0.05-<br>0.10 mg. |
| New Orleans | 6 (8%) | 1 (1%) | 12 | 240 - 399<br>Av. 303 | 1.9 | 0.025 mg. |
| Los Angeles | 0 (0%) | 0 (0%) | -- | 26 - 178<br>Av. 81 | 1.8 | --- |
| San Francisco | 5 (7%) | 3 (4%) | 12 | 110 - 220<br>Av. 170 | 1.4 | 0.025 mg. |
| Cincinnati | 6 (8%) | 3 (4%) | 12 | 278 - 1490<br>Av. 940 | 1.5 | 0.25 mg. |
| Detroit | 4 (6%) | 4 (5%) | 15 | 730 - 1580<br>Av. 1176 | 1.2 | 0.025 mg. |
| Philadelphia | 5 (7%) | 4 (5%) | 18 | 310 - 682<br>Av. 449 | 1.5 | 0.025 mg. |

Table 26

Lung Cancer Death Ratios

Coke Oven and Gas Retort Workers

| Author | Country | No. Cases | Mortality Rates |
|---|---|---|---|
| Kawahata | Japan | 21 | 500 |
| Doll | England | 97 | 284 (Gas Stokers, Coke Oven Chargers) |
| | | | 202 (Gas Producer men) |

population at risk but does not result in a complete abolition of a cancer hazard, unless extremely low degrees of exposure prevail. The observations reported in connection with this study and made on mice given graduated doses of 3.4-benzpyrene provide a striking illustration of this basic principle.

Consideration, moreover, must be given to the fact that the degree of carcinogenic response to a given dose of a carcinogen is distinctly higher when it is administered in fractionated repeated doses than when it is given as a single dose. It is exactly the often-repeated and prolonged type of exposure to atmospheric carcinogens which exists for the inhabitants of urban and industrialized areas, who inhale the polluted air from birth to death, and thereby introduce constantly into their respiratory system small amounts of carcinogenic hydrocarbons, which over the years exert a cumulative effect upon the exposed bronchial mucosa.

This effect, either alone or in combination with additive reactions to the same or other chemically similar carcinogens inhaled for other reasons, may well cause or contribute to the development of lung cancers in some members of the urban population at risk, especially since respiratory contact with such carcinogenic hydrocarbons is for the urban population more severe and prolonged from air pollutants than from any other source, with the exception of some special occupational conditions.

Considering that carcinogenic hydrocarbons furnish doubtlessly important fractions of the total carcinogenic air pollution, the observed marked increases of lung cancer rates in urban communities following the rise in the degree of atmospheric pollution from industrial and industry-related sources provide weighty epidemiologic evidence supporting the existence of causal relations between these phenomena.

The evidence on hand thus makes it likely that carcinogenic air pollutants of the chemical types and sources studied in this investigation have played an important role in the progressive increase of the frequency of lung cancers during recent decades. It should be emphasized, however, that neither the methods and the results of the bioassays of the four fractions studied nor the results of the chemical analyses of the four fractions permit any valid conclusions concerning their exact quantitative role in this respect in any particular community, nor in urban communities and conurbations as a whole. One important basic requirement which would have to be met before such interpretations would be possible is the availability of much more comprehensive and reliable data on the incidence rates of lung cancer among members of occupations exposed during their work to these agents (table 27) than exist so far.

In fact, observations made in the field of occupational lung cancer hazards, together with the results of recent chemical analyses of the inorganic chemical constituents of the particulate phase of urban air-pollutants, make it not improbable also that some of these pollutants may have contributed significantly, at least in some cities, to the total atmospheric lung cancer hazards from general and occupational air pollutants. Several epidemiologic studies of lung cancer death rates among members of

several large worker groups indeed have revealed an excessive liaibility to lung cancer in workers exposed to ferrous and non-ferrous metal dusts and fumes (tables 28 and 29) (Mancuso; Morrison). There exists also a great deal of trustworthy evidence incriminating an occupational inhalation of several specific metals and minerals, such as radioactive substances, arsenicals, chromium, nickel and iron compounds, and asbestos in the occurrence of highly elevated lung cancer rates among members of several occupational groups (table 30). It is characteristic that some of these agents, i.e., radioactive substances, nickel, chromium arsenicals, moreover, seem to be responsible for the development of cancers of other parts of the respiratory tract, especially the nasal activity and the nasal sinuses. This observation fits well into the general exposure pattern prevailing for some of the worker populations at risk (tables 31, 33, 34, 35, 36). Supporting these observations in man, experimental investigations have established the carcinogenicity of several of these inorganic chemicals, such as radioactive substances, chromates, nickel and nickel salts for animals. It may be mentioned here that adequate and valid epidemiologic and medical evidence attests to the carcinogenic action of arsenicals and asbestos in man.

The carcinogenic role which these substances might assume as general air pollutants becomes apparent from a few industrial observations as well as from the results of recent studies on inorganic chemical air pollutants by the Sanitary Engineering Center (table 33). Some of the early German observations on industrial chromate cancers of the lung, for instance, showed that lung cancer hazards existed not only for workers directly employed in the manufacture of chromates but also for workers employed mainly outside of such establishments, such as yard workers, truckers, etc., or even in adjacent buildings located within the fume and dust zone of the chromate operations. In view of the considerable dilution factor concerning an exposure to atmospheric chromium compounds which must have prevailed under such circumstances, these findings are indicative of, in addition to the highly excessive lung cancer rates among the chromate workers proper, the marked carcinogenic potency of certain chromium compounds generated during the production of chromates or released as dust into the air from the chromium-containing slag heaps often found outside of the factory buildings. The range of general atmospheric pollution with chromium from such sources is apparent from the study of Bourne and Yee conducted in the environment of a plant in Ohio (fig. 8). It is even more strikingly illustrated by the data published by the Sanitary Engineering Center as part of the air pollution measurements of the National Air Sampling Network carried out from 1953 to 1957. The air of Baltimore, where the largest American chromate factory is located, showed minimal chromium values of .023 micrograms of chromium per cbm., of air, and maximal values of .290 micrograms. Several other industrial cities, some with steel plants or oil refineries, had maximal values between .100 and .200 micrograms (Pittsburgh, Louisville, East Chicago, Denver). The average American city, on the other hand, exhibited maximal values between .002 and .040 micrograms.

Perhaps even more impressive are the highly excessive values for nickel obtained in the atmospheric pollutants of Waterbury, Connecticut. Its atmospheric nickel level stood as high as 2.800 micrograms against the next maximal highest level of .300 in Boston as compared with values between .005 and .100 micrograms for most other cities studied. These few data may suffice

Table 27

Frequency of lung cancer among operating and nonoperating railroad workers

| Railroad | Period | Total Lung Cancers | Type of railroad worker: Operating Number | Operating Percent | Nonoperating Number | Nonoperating Percent | Undetermined Number | Undetermined Percent |
|---|---|---|---|---|---|---|---|---|
| A | 1940-50 | 29 | 24 | 83 | 5 | 17 | --- | --- |
| B | 1939-49 | 104 | 59 | 57 | 15 | 14 | 30 | 29 |

Table 28

Standard Mortality Rates of Malignant Neoplasms of the Respiratory System in Occupational Classes in Scotland (Morrison)

| Occupational Code No. | Occupation | SMR |
|---|---|---|
| | | Above 130 |
| 160-164 | Platers, riveters, shipwrights | 183 |
| 231-249 | Electrical apparatus makers, electricians | 170 |
| 131, 132 | Moulders | 162 |
| 589 | Masons and stone cutters | 162 |
| 134-138 | Foundry workers, etc. | 161 |
| 681 | Dock laborers | 157 |
| 912 | Crane drivers | 150 |
| 600-609 | Painters, decorators | 132 |
| | | Below 70 |
| 019, 021, 029 | Farm workers | 25 |
| 010, 011, 018, 020 | Farmers, etc. | 27 |
| 110-119 | Foremen & overlookers in metal manufacture | 54 |
| 013-015 | Market or other gardeners | 56 |
| 620-629 | Managers of industrial undertakings other than managers of office departments | 69 |

Table 29

Lung cancer death rates per 1,000 deaths from all causes for 7 industrial groups in Ohio, 5,309 males, 1947 (Mancuso)

| Industry | Death rate |
|---|---|
| Nonferrous metal | 3.22 |
| Transportation | 2.91 |
| Rubber and plastics | 2.34 |
| Iron and steel | 2.18 |
| Mining and quarrying | 1.53 |
| Agriculture | .82 |
| Stone, clay, glass | .66 |
| Total | 1.76 |

Table 30

Specific worker groups
with specific respiratory cancer hazards
from metals and minerals

| Agent | Worker Groups |
|---|---|
| Asbestos | Asbestos miners, textile workers. |
| Arsenic | Manufacturers, handlers, and users of arsenical insecticides; arsenic smelter workers; taxidermists; sheep dip workers; copper smelter workers. |
| Chromium | Chromate manufacturers including plant maintenance workers; chrome pigment handlers. |
| Nickel | Nickel-copper matte refinery workers. |
| Iron | Iron ore (hematite) miners? Iron foundry workers. |
| Radioactive Substances | Radioactive ore (pitchblende) miners; miners of non-radioactive ores working in radioactive mines. |

Table 31

Chronic Arsenicism and Cancers Among Vineyard Workers of the Moselle Valley

| Cases | Cause of Death | Ferd. Roth<br>Coexisting Cancers | Cases with Cancers | Total Number of Cancers |
|---|---|---|---|---|
| 16 | Bronchiogenic Carcinoma with Cirrhosis of Liver | 2 cases with 1 skin cancer<br>1 case with 2 skin cancers<br>1 case with 3 skin cancers<br>2 cases with 4 skin cancers | 16 | 31 |
| 2 | Double Carcinomas of Lung | 1 case with 1 larynx cancer and 1 skin cancer<br>1 case with 1 skin cancer | 2 | 7 |
| 1 | Bile Duct Carcinoma | 1 case with bronchiogenic carcinoma | 1 | 2 |
| 6 | Sarcoma of Liver with Cirrhosis | 1 case with 2 skin cancers | 6 | 8 |
| 5 | Esophageal Carcinoma with 2 Cirrhosis of Liver | 1 case of carcinoma of tongue<br>1 case with 3 skin cancers | 5 | 9 |
| 8 | Cirrhosis of Liver | 1 case with 5 skin cancers | 1 | 5 |
| 1 | Arsenicosis | 1 case with 5 skin cancers | 1 | 5 |
| 1 | Chronic Bronchitis | 1 case with 5 skin cancers | 1 | 5 |
| 7 | Miscellaneous Diseases | | 0 | 0 |
| 47 | | | 33 | 72 |

## Table 33

Range of Maximum Metal Levels in Selected Cities. ( Tabor and Warren).

| Metal | City | Low Level Microgram/cbm | High Level Microgram/cbm | City |
|---|---|---|---|---|
| Zinc | Fort Worth | 0.4 | 49.00 | Chicago |
| Iron | Lakehurst | 0.23 | 30.00 | East Chicago |
| Copper | Washington | 0.05 | 30.00 | Boston C |
| Lead | Lakehurst | 0.33 | 17.00 | Boston |
| Manganese | Lakehurst and Paulsboro | 0.01 | 3.00 | Chattanooga |
| Barium | Lakehurst and Paulsboro | 0.005 | 1.50 | Houston |
| Tin | Tampa | 0.004 | 0.80 | Boston |
| Vanadium | Fort Worth | 0.002 | 0.60 | Jersey City |
| Titanium | New Orleans and Tampa | 0.01 | 0.24 | East Chicago |
| Nickel | Houston C | 0.005 | 0.24 | East St. Louis-N. Y. |
| Chromium | Lakehurst | 0.002 | 0.12 | East Chicago |
| Cadmium | Boston | 0.002 | 0.10 | East St. Louis |
| Bismuth | Boston C Minneapolis | 0.002 | 0.03 | New York |

Table 34

Lung Cancer Rates in Chromate Workers

| Country | Expected | Frequency Observed | Frequency Rate per 100,000 | |
|---|---|---|---|---|
| | | | Chromate Workers | General Population |
| United States | 1.9 | 31.9 | 470.8 | 16.7 |
| Germany | 1.0 | 43.0 | | |
| England | 1.3 | 7.0 | | |

Table 35

Siderosis of Lung and Cancer of Lung in English Hematite Miners and Iron Foundry Workers

| Author | Occupation | No. of Autopsies | No. of Lung Cancers | Percentage |
|---|---|---|---|---|
| MCLaughlin and Harding | Iron Foundry Workers | 149 | 16 | 10.8 |
| Faulds and Stewart | Hematite Miners | 180 | 17 | 9.4 |
| Harding and Massie | Boiler Scalers | 12 | 3 | 20.0 |
| Faulds and Stewart | Controls | 2220 (Over 30 Years) | 45 | 2.0 |

Table 36

Causes of death among male asbestos workers compared with the mortality experience of all men in England and Wales (Doll)

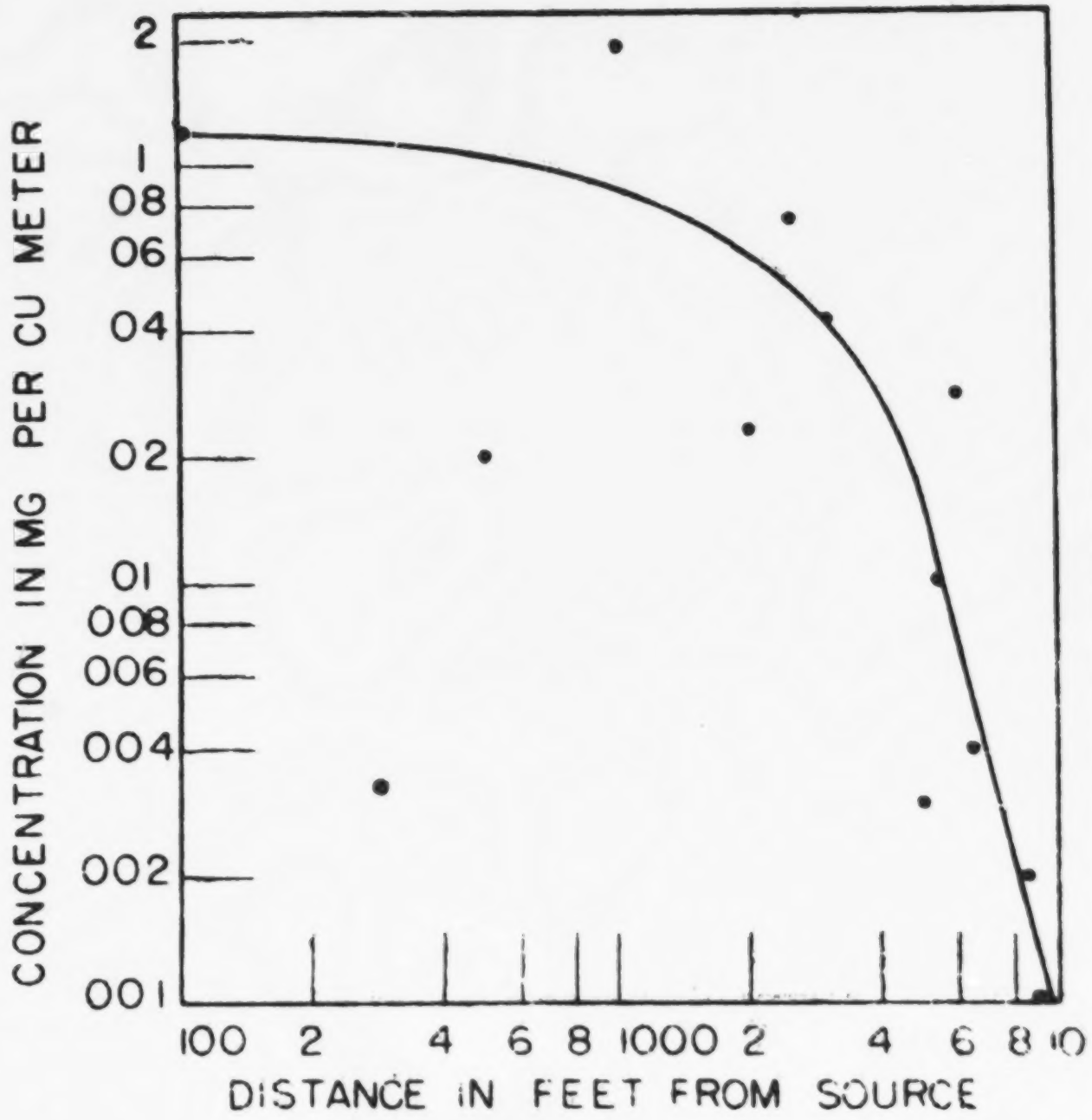
| Cause of death | Number of deaths | | Test of significance of difference between observed and expected (value of P.) |
|---|---|---|---|
| | Number observed | Expected on England and Wales rates | |
| Lung cancer [1] | 11 | 0.8 | < 0.000001 |
| Other respiratory diseases [2] and cardiovascular diseases— | | | |
| With mention of asbestosis | 14 | | < 0.001 |
| Without mention of asbestosis | 6 | 7.6 | |
| Neoplasms, other than lung cancer | 4 | 2.3 | |
| All other diseases [3] | 4 | 4.7 | > 0.1 |
| All causes | 39 | 15.4 | < 0.000001 |

[1] Including 1 case with pulmonary tuberculosis.

[2] Including pulmonary tuberculosis.

[3] Including 2 cases (benign stricture of esophagus and septicaemia) in which asbestosis was present but was not thought to have been a contributory cause of death.

Fig. 8


CONCENTRATION IN MG PER CU METER
2
1
08
06
04
02
01
008
006
004
002
001
100
2
4
6
8
1000
2
4
6
8
10
DISTANCE IN FEET FROM SOURCE

for indicating the scope of these aspects of potential general atmospheric air pollutants and the need for future investigations in such matters. Doubtlessly the concentrations of such carcinogenic chemicals can be expected to be much higher in the immediate neighborhood of the industrial establishments responsible for such atmospheric pollutions. One may likewise justly assume that any lung cancer hazards possibly related to contaminations of the air from such sources will be much more severe for the population living and working in the immediate neighborhood of such plants. The present studies have also not included a consideration of atmospheric air pollutants present in a gaseous or vaporized state. It is essential that in any future study the factor of atmospheric radioactivity as a primary or contributory agent to the formation of lung cancers be properly investigated. These carcinogenic agents which from a viewpoint of lung cancer hazards were until rather recently mainly of strictly occupational importance have assumed more general importance not only for occupational reasons but also as carcinogenic atmospheric pollutants. No worthwhile information exists also on the possible carcinogenic significance of other air pollutants present in the gaseous or vapor phase, especially those of organic chemical nature. Experimental studies of such factors have been limited for technical reasons (Kotin and Falk). Perhaps this facet of air pollution may successfully be attacked by investigating and applying conditions which determine the formation and quantity of aqueous and oily condensation nuclei in the air, since these nuclei tend to produce foci of increased preferential concentration of certain chemicals present in the air. They may alter thereby fundamentally the type and degree of exposure of the bronchial mucosa. Chemicals concentrated in such nuclei do not reflect the overall and uniform concentration of such chemicals in an atmosphere free from condensation nuclei (Barklie). Future studies may well include, moreover, an investigation of the role which ionization and electrical charge of particles may play in their retention on the respiratory mucosa.

It will be necessary, moreover, to assess the possible role of other chemicals recently introduced into the human environment which possess carcinogenic properties for man and/or animals. Carbamates, beta-propiolactone, aromatic amines, chlorinated hydrocarbons, and various carbon and silicon polymers and plastics, for instance, deserve attention in this direction.

Mankind has chosen since many decades, and to an increasing degree during more recent years, to complicate further these complex atmospheric exposure conditions sustained for general environmental as well as occupational reasons, by adding its personalized type of carcinogenic exposure through indulging in the tobacco smoking habit, especially the more recently introduced form of smoking cigarettes. The great number of claims concerning the predominant importance of cigarette smoking in the causation and rise in frequency of lung cancers, ranging from 60 to 96% of all lung cancers in males, are evidently products of a rather selective type of research and of deliberate reasoning from a limited and special kind of evidence.

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The voluminous reports on this subject published during recent years give, in general, scant consideration to the influence which non-tobacco factors may have exerted on the causation and that rise in frequency of lung cancers, which started before cigarette smoking became generally popular. While it is quite likely that cigarette smoking has played a direct or indirect role in this respect, it is, on the other hand, not probable that it was of overwhelming importance as alleged by many investigators. The following reasons militate against such a claim:

1. The increase in the frequency of lung cancers started on the European continent before cigarette smoking assumed in these countries significant proportions.

2. The marked irregularity of the lung cancer mortality rates, of their progression rates, and of their sex distribution rates in different countries, different regions and different metropolitan areas of the same country, militate strongly against a predominant causal action of a single factor such as cigarette smoking.

3. The consistent discrepancy between high urban lung cancer rates against low rural rates observed in several countries carries the same connotation.

4. The definite differences in the lung cancer rates between native and immigrant whites observed in New Zealand, South Africa and Ohio despite presumably similar smoking habits, does not favor the concept of a major role of cigarette smoking in the causation of lung cancer.

5. The absence of a positive statistical relation of cigarette smoking to cancers of the hands and lips which become intensely exposed to incomplete combustion products of cigarette tobacco, represents evidence which disagrees with observations made among individuals exposed to coal tar fumes and dusts and developing cancers of the skin and lung.

The far reaching contentions made in favor of the cigarette theory of lung cancer causation read rather convincingly as long as one either does not know or conveniently neglects to critically consider the indeed large and reliable amount of evidence that is in disagreement with such concepts offered often as facts and proof. It should be obvious to any open-minded observer that the results of a critical assessment of the general as well as local epidemiologic pattern of lung cancers cannot be reconciled with the claims advanced by the protagonists of the cigarette theory, since they cannot reasonably account for the marked and striking irregularities of this pattern described in the first part of this presentation. The cigarette theory can also not plausibly and scientifically explain some etiologically important symptomatic characteristics related to carcinogenic responses in smokers without taking recourse to some rather artificial auxiliary hypotheses of most dubious scientific merits. Among these one may mention the assumption of a special affinity and/or resistance of certain tissues to the carcinogenic action of cigarette tar (bronchial mucosa versus oral and labial mucosa). Recent studies on the occurrence, frequency and distribution of atypical and metaplastic local reactions in

the tracheal and bronchial mucosa of individuals of all ages and with different disease conditions have not confirmed the much publicized contention of a close and consistent relation of cigarette smoking to these so-called precancerous lesions (Hackensellner; Kinsella; Sanderud; Kinsella). It is evident from subsequent investigations that many other irritants of the bronchial mucosa, and not only cigarette smoke, exert a similar effect. In fact, one investigator noted that such lesions are not infrequently present in children. A definite amount of reservation is indicated in accepting the claims advanced by some parties concerning the role of cigarette smoking as a direct or indirect factor in the causation of lung cancer. Nevertheless the type and amount of evidence on this matter on hand justifies the conclusion that cigarette smoking has contributed to or aggravated the action of other carcinogenic respiratory pollutants by producing especially functional disturbances in the bronchial mucosa, as recently shown by Tremer, Falk and Kotin. It would be most unwise, on the other hand, if, through an exaggerated emphasis placed on the significance of cigarette smoking, the study of general and local industry-related air pollutants would be impaired and neglected. The available evidence rather definitely assigns to these factors an important role as human respiratory carcinogens. The obvious and proven lung cancer hazards related to these agents deserve serious attention especially since they can be controlled by proper sanitary and technologic measures.

## Conclusions

1. Bioassays performed on mice with four subcutaneously injected solvent fractions of the particulate phase of air pollutants of eight cities containing aromatic as well as aliphatic hydrocarbons, yielded cancerous reactions with all four fractions.

2. The cancer yield obtained by the various fractions differed with the fraction as well as with the city from which the air-pollutants were collected.

3. With the exception of air pollutants of Birmingham, which showed the highest total cancer yield and which had also the highest amount of 3.4-benzpyrene, there was no consistent correlation between the degree of carcinogenic potency of the solvent fractions bioassayed, the amount of 3.4-benzpyrene, and the reported lung cancer mortality rate in the eight cities studied.

4. It appears that every community has an atmospheric carcinogenic spectrum which depends upon local conditions which include not only industrial activities and traffic conditions, but also climate, solarization, and geologic conditions.

5. An exploration of the relative role and importance of these factors for the lung cancer panorama of individual cities should include an investigation not only of the aromatic and aliphatic hydrocarbons present in the particulate phase of air pollutants but also of metallic, mineralic and radio-

active constituents as well as the relative chemical stability and the physical status of some of these elements in the atmosphere.

6. The present studies represent merely a first and preliminary step in a prolonged and comprehensive program dealing with relationship between air pollutants and health hazards, including cancers.

Bibliography

1. Bourne, H.G. and Yee, H. T., Occupational Cancer in a Chromate Plant: An Environmental Appraisal. Indust. Med. & Surg. 19:568-572,1950.

2. Doll R., Etiology of Lung Cancer.Adv. Cancer Res. 3:1-51,1955.

3. Faulds, J. S. and Stewart, M.J., Carcinoma of the Lung in Hematite Miners. J. Path. & Bact. 72:353-366,1956.

4. Hueper, W.C., A Quest into the Environmental Causes of Cancer of the Lung. Publ. Health Monograph No. 36, U.S. Public Health Service Publication 452,1956,p.54.

Role of Occupational and Environmental Air Pollutants in Production of Respiratory Cancers. Arch. Path. 63:427-450,1957.

Luftverunreinigungen und Krebs. Krebsforsch.u.Krebsbek. 3:162-189,1959.

5. Kotin,P. et al., Aromatic Hydrocarbons. I. Presence in the Los Angeles Atmosphere and the Carcinogenicity of Atmospheric Extracts. Arch. Indust. Hyg. & Occup. Med. 9:153-163,1954.

II. Presence in the Particulate Phase of Gasoline Engine Exhausts and the Carcinogenicity of Exhaust Extracts. Arch. Indust. Hyg. & Occ. Med. 9:164-177,1954.

III. Presence of Particulate Phase of Diesel-Engine Exhaust and the Carcinogenicity of Exhausts Extracts. Arch. Indust. Hyg.& Occ.Med. 11:113-125,1955.

6. Kuroda, S. and Kawahata, K., Ueber gewerbliche Entstehung des Lungenkrebses bei Generatorgasarbeitern. Zeitschr.f.Krebsf. 45:36-39,1936.

7. Leiter,J. and Shear, M.J.,Production of Tumors in Mice with Tars from City Air Dusts.

J.Nat.Cancer Inst 3:167-173,1942.

8. McLaughlin,A.I.G. and Harding, H.E.,Pneumoconiosis and Other Causes of Death in Iron and Steel Foundry Workers. Arch.Indust.Health 14:350-378, 1956.

9. Mancuso, T.F.,MacFarlane,E.M. and Porterfield, J.D., Distribution of Cancer Mortality in Ohio. Am.J.Publ.Health.45:58-70,1955.

10. Morrison,S.L., Occupational Mortality in Scotland. Brit. J.Indust.Med. 14:130-132,1957.

11. Roth, F.,Ueber den Bronchialkrebs arsengeschaedigter Winzer. Virchows Arch. 331:119-137,1958.
Ueber die chronische Arsenvergiftung der Moselwinzer unter besonderer Berücksichtigung des Arsenkrebses. Zeitschr.f.Krebsf. 61:287-319,1956.

12. Sawicki,E.,Elbert,W.,Houser,T.R.,Fox,F.T. and Stanley,T.W., The Benzo(A) Pyrene Content of the Air of the United States. Am. Indust. Hyg. Ass. J. in press.

13. Stocks, P. and Campbell,J.M., Lung Cancer Death Rates Among Non-Smokers and Pipe and Cigarette Smokers. An Evaluation in Relation to Air Pollution by Benzpyrene and Other Substances. Brit.Med.J. ii:923-933,1955.

14. Tabor,E.C. and Warren,Wm.V.,Distribution of Certain Metals in the Atmosphere of Some American Cities. Arch. Indust.Health.17:145-151,1958.

15. Waller, R.E., The Benzpyrene Content of Town Air. Brit.J.Cancer.6:8-21.1952.

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